DEVELOPMENT OF NEW SYNTHETIC METHODOLOGY AND STUDIES DIRECTED TOWARDS THE SYNTHESIS OF TRICYCLOPENTANOIDS

A Thesis Submitted

In Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

By

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to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

DECEMBER, 1988

DEDICATED

TO

MY PARENTS

STATEMENT

I hereby declare that the matter embodied in this thesis, "Development of New Synthetic Methodology and Studies Directed Towards the Synthesis of Tricyclopentanoids", is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Prof. S. Chandrasekaran.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

N·

(N. CHIDAMBARAM)

Kanpur:
December 1988

CERTIFICATE

Certified that the work, "Development of New Synthetic Methodology and Studies Directed Towards the Synthesis of Tricyclopentanoids", presented in this thesis has been carried out by Mr. Nallaperumal Chidambaram under my supervision and the same has not been submitted elsewhere for a degree.

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CERTIFICATE OF COURSE WORK

This is to certify that Mr. Nallaperumal Chidambaram has satisfactorily completed all the courses required for the Ph.D. degree program. The courses include:

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Chm 511 Physical Organic Chemistry

Chm 524 Modern Physical Methods in Chemistry

Chm 525 Principles of Physical Chemistry

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Chm 801 Graduate Seminar

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PREFACE

The thesis entitled "Development of New Synthetic Methodology and Studies Directed Towards the Synthesis of Tricyclopentanoids" is divided into two major chapters and each chapter is further divided into two parts. Part A in chapter I is subdivided into four sections as outlined below.

<u>Chapter I</u> :

Part A   : Studies of oxidation with Pyridinium dichromate / t-Butylhydroperoxide.

    (i) A convenient reagent for allylic and benzylic oxidations

    (ii) Oxidation of Enol ethers with PDC/t-BuOOH

    (iii) Application of the present strategy to the synthesis of α-Pyrone 4, ($\pm$) Argentilactone 25 and ($\pm$) Goniothalamin 27

    (iv) Facile and selective deoximation of ketoximes

Part B   : Reaction of allylic and benzylic esters with low valent titanium reagents.

<u>Chapter II</u> : Synthesis of linearly fused tricyclopentanoids

Part A   : Intermolecular cycloaddition approach

Part B   : Intramolecular Vinylketene-Olefin cycloaddition approach

Part A - (i) in chapter I deals with the development of a new reagent system pyridinium dichromate/t-butylhydroperoxide for effecting allylic and benzylic oxidations. A number of methods are currently available in literature for allylic and benzylic oxidations. Still there is a need for developing a new reagent system to effect these oxidations with ease and selectivity. Pyridinium dichromate or t-butylhydroperoxide does not oxidize allylic and benzylic positions independently, but when they are mixed in a 1:1 ratio it turns out to be an excellent reagent for allylic and benzylic oxidations.

1-Phenylcyclohexene gives exclusively 2-phenylcyclohex-2-enone 8 and limonene gives piperitenone 16 as the only product (none of carvone and isopiperitenone). Cycloheptene gives in addition to cyclohept-2-enone 14, cyclohept-2-enyl-t-butyl hydroperoxide 14a. With excess reagent cyclohept-2-enyl-t-butyl hydroperoxide 14a is oxidized to cyclohept-2-enone 14. Benzylic oxidations with this reagent system generally gives high yields of products .

In section(ii) of Part A chapter I reactivity of PDC/t-BuOOH reagent system with enol ethers has been studied. Dihydropyran on treatment with this reagent system yields dihydro-α-pyrone 3 as the only major product in addition to small amount of 2-t-butyl-peroxo-5,6-dihydropyran 2. Enol ether 7 on treatment with PDC / t-BuOOH gives 8 and 9. Under the same reaction conditions, acyclic enol ethers give esters. For example 1-ethoxy- heptene

and 1-ethoxyoctene give ethylheptanoate and ethyloctanoate respectively.

Section (iii) of Part A chapter I describes the application of this oxidative rearrangement methodology for the synthesis of some natural products . α-Pyrone skeleton is present in flavanoids and it is a butadiene equivalent. In the present study α-pyrone 4 has been synthesized from dihydropyran in good yield. (+) Argentilactone 25 is a constituent of species aristolochia argentina and (+) goniothalamin 27 a constituent of species goniothalamus macrophyllus contain dihydro-α-pyrone unit as part of the molecular framework. Our methodology of oxidative rearrangement of enol ethers with PDC/t-BuOOH has been efficiently used as the key step in the synthesis of these natural products .

Section (iv) of Part A of chapter I reports the utility of this reagent system for the selective regeneration of carbonyl compounds from oximes. PDC / t-BuOOH reagent system selectively regenerates carbonyl compounds from ketoximes in preference to aldoximes. 2,4-DNP derivatives have been found to be inert to this reagent . Although this reagent system generally effects allylic and benzylic oxidations, deoximation is more facile and can be performed easily on molecules which contain carbon-carbon double bonds and benzyl groups.

In Part B of chapter I we have explored the reactivity of low valent titanium reagent Ti^{+2} derived from TiCl$_4$ Mg/Hg towards allylic and benzylic esters of carboxylic acids 7, 23 and 1. Since these reactions are believed to proceed via electron transfer mechanism, allylic and benzylic esters are expected to give the corresponding carboxylic acids. In addition to the expected carboxylic acids, deoxygenation is observed to give the corresponding hydrocarbons 2, 8 ,24 and aryl allyl ketones 3 ,9 and 25 .

Chapter II describes studies directed towards the synthesis of linearly fused tricyclopentanoids from readily available starting materials. Part A of this chapter deals with an intermolecular (2+2) cycloaddition approach starting from 3-methylindene 17. The aromatic ring in 21 is subjected to Birch reduction. After forming the vicinyl diol, catalytic hydrogenation affords the cis-anti-cis tricyclic ring system 24 and ring contraction leads to the key tricyclopentanoid intermediate 31.

In another approach the readily available cyclo- adduct 32 from cyclopentadiene and maleic anhydride has been converted to the spirolactone 33 which on rearrangement with acid yields the ketoenone 36. Further chemical manipulations lead to the functionlized tricyclopentanoid 38.

In the third approach endo-dicyclopentadiene has been transformed to the cis-anti-cis tricyclopentanoid carbon skeleton 42 .

Part B of chapter II deals with the development of an intra-molecular vinylketene-olefin cycloaddition approach for the construction of bicyclo [3.2.0] heptane skeleton 57 from 55 which then was converted to 58, a key intermediate in the synthesis of (+) hirsutene 3 .

TABLE OF CONTENTS

C H A P T E R   I

Part A : STUDIES OF OXIDATION WITH PYRIDINIUM DICHROMATE/ t-BUTYLHYDROPEROXIDE

A convenient reagent for allylic and benzylic oxidations

I.1.a   Introduction

Development of new reagent systems and synthetic methodologies form an integral part of organic synthesis. Among the various transformations, oxidation and reduction of various functional groups are the most important transformations employed by an organic chemist.

A number of reagents are currently available for allylic and benzylic oxidations[1] using Cr(VI) complexes. Besides the commonly used reagents the methodologies developed in recent years are of interest. Since each reagent so developed has been used to better the existing oxidising agents and also used to manipulate certain specific transformations.

Pearson and co-workers[2] have developed a reagent system, t-butyl hydroperoxide-chromium hexacarbonyl catalyst, for effecting allylic oxidations in fairly good yields in the presence of secondary alcohols (Scheme I. A. 1)

When our investigation on the utility of the newly developed reagent system was in progress, a paper by Muzart[3] appeared in the literature utilising anhydrous t-butyl hydroperoxide-2,4-dimethyl-pentane-2,4-diol cyclic chromate catalyst for benzylic

SCHEME I.A.1[2]

Compound **1** → Cr(CO)$_6$ / t-BuOOH → **2**

Compound **9** → ,, → **10**

Compound **15** → ,, → **23** + **24**

SCHEME I.A.2[3]

Compound **17** → anhyd. t-BuOOH → **18** + **18a**

Compound **19** → ,, → **20**

Compound **21** → ,, → **22**
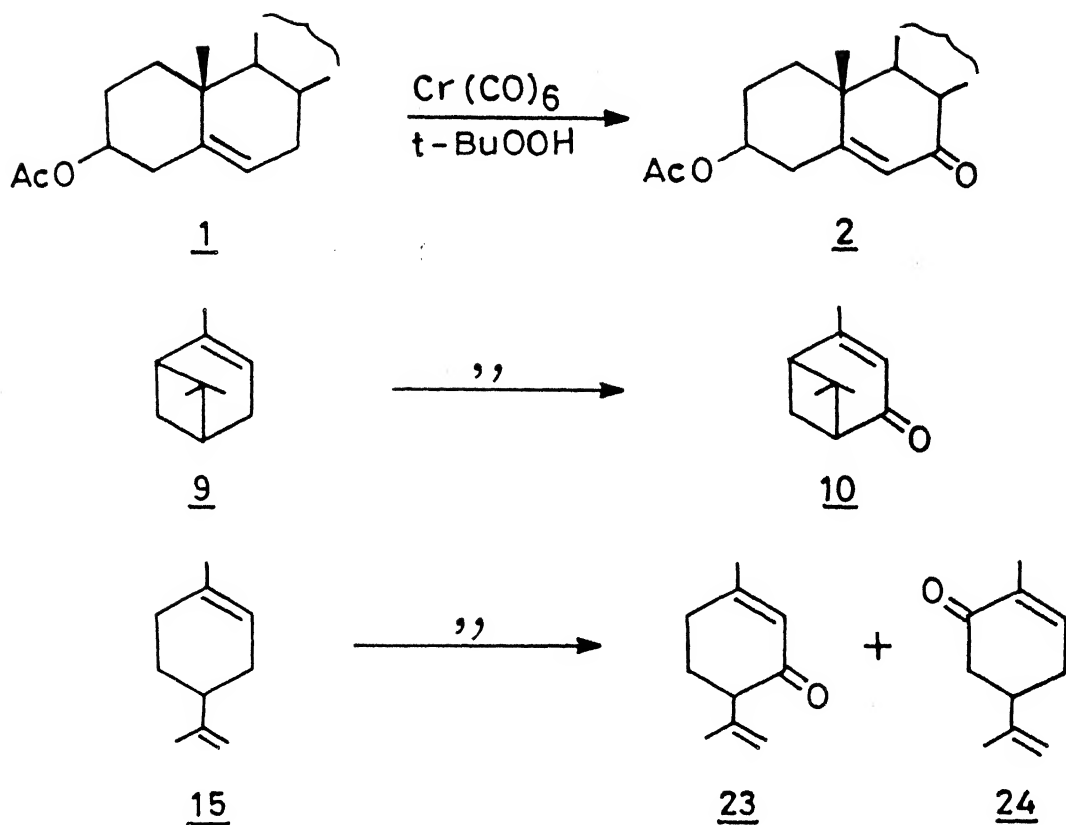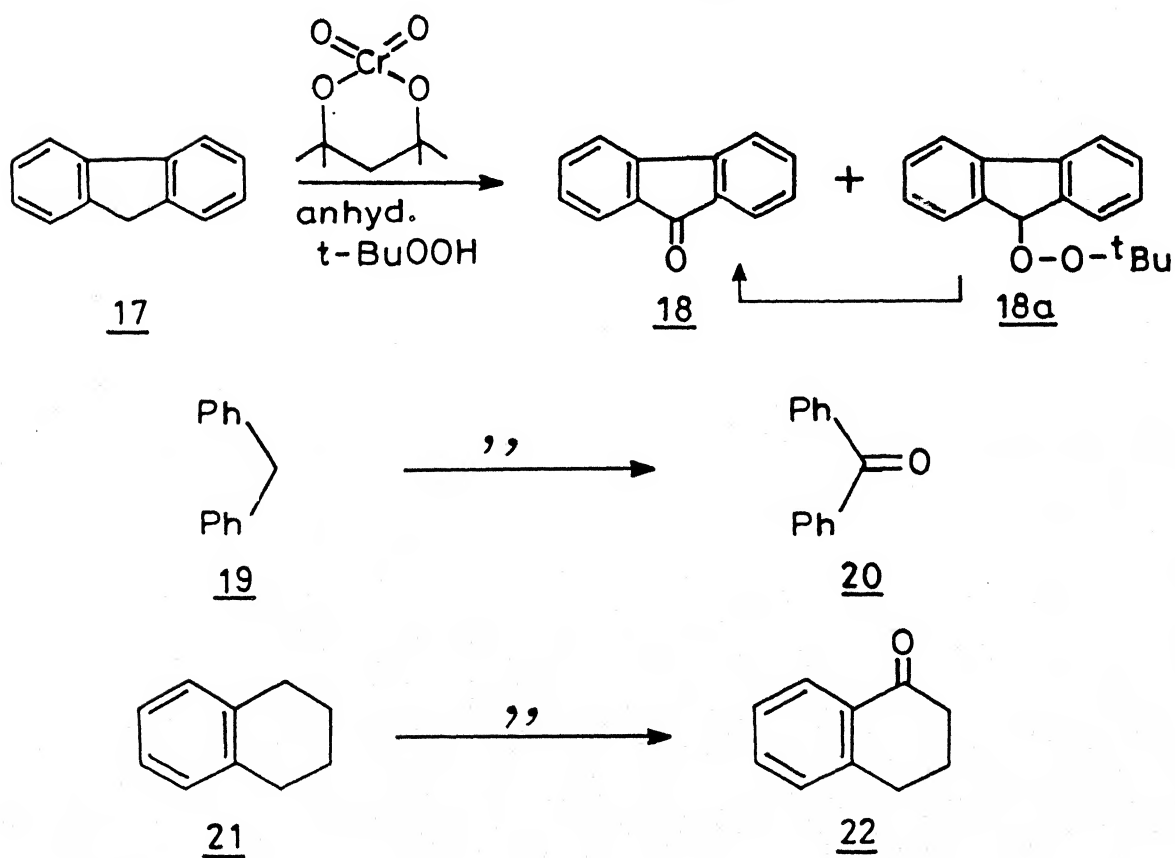
oxidations. He later reported that chromium trioxide can be substituted for 2,4-dimethylpentane-2,4-diol cyclic chromate catalyst which along with 70% t-butyl hydroperoxide effects benzylic oxidations[4] (Scheme I. A. 2 and I. A. 3).

Muzart has explored the utility of this reagent system for allylic oxidations also[5] (Scheme 1. A. 4). Although these are good oxidising agents, the former one using $Cr(CO)_6$ is very toxic and environmentally hazardous. The latter one by Muzart would definitely serve as good oxidising agent for benzylic and allylic oxidations.

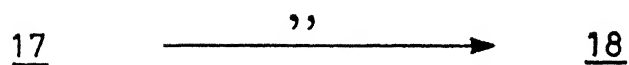Earlier report from our laboratory has shown the utility of Cr(VI) reagent (pyridinium chlorochromate)[6] for allylic[7] and benzylic[8] oxidations. Though the products were obtained in high yields, long reaction time and refluxing conditions are required (Scheme I. A. 5 and I. A. 6).

Reagents are available in good numbers for benzylic oxidations but very few for allylic oxidations. Owing to the limitations of the available reagents, there exists a need for effecting these oxidative transformations under mild conditions with high degree of selectivity. With this in mind we set out to develop a reagent system that would simplify the reaction conditions and at the same time impart selectivity.

SCHEME I.A.3[4]

$\underline{21} \xrightarrow[\text{70\% t-BuOOH}]{\text{CrO}_3} \underline{22} + $ 22a

$\underline{17} \xrightarrow{\text{,,}} \underline{18}$

SCHEME I.A.4[5]

$\underline{1} \xrightarrow[\text{70\% t-BuOOH}]{\text{CrO}_3} \underline{2} + $

2a

27   28   29

30   31   32

R = Ph

= $C_{17}H_{35}$

SCHEME I.A.5[6]

7       $\xrightarrow[\text{CH}_2\text{Cl}_2,\ \triangle]{\text{PCC}}$ 8

15       $\xrightarrow{\text{''}}$ 23   +   24

SCHEME I.A.6[7]

21       $\xrightarrow[\triangle]{\text{PCC, Benzene}}$ 22

19       $\xrightarrow{\text{''}}$ 20

25       $\xrightarrow{\text{''}}$ 26
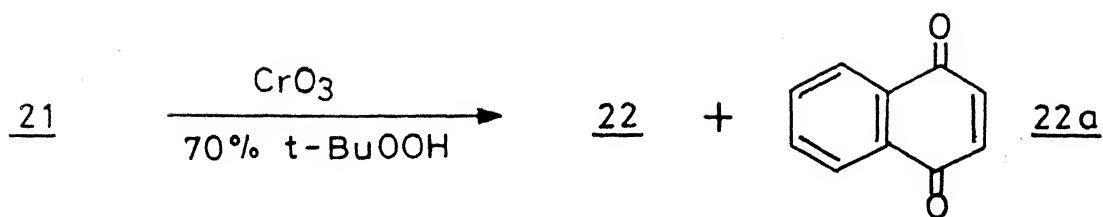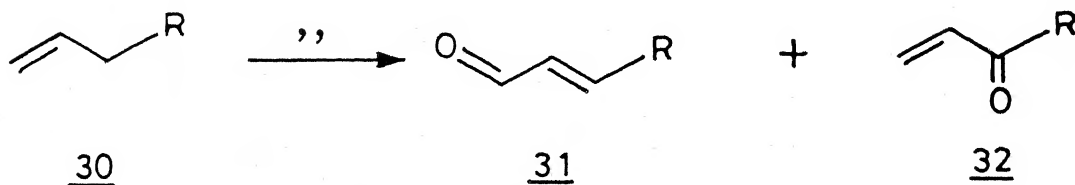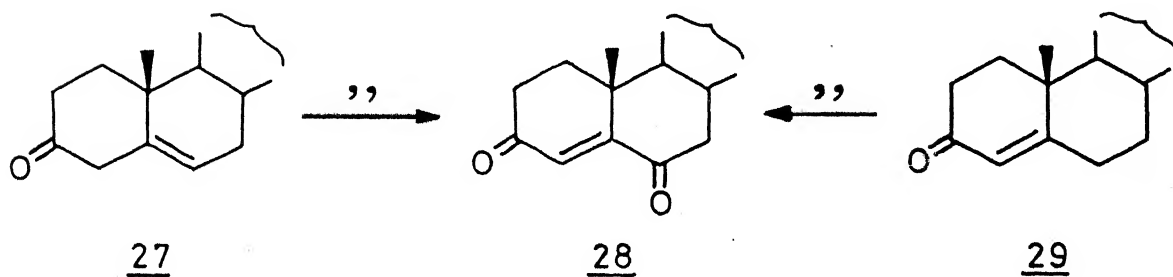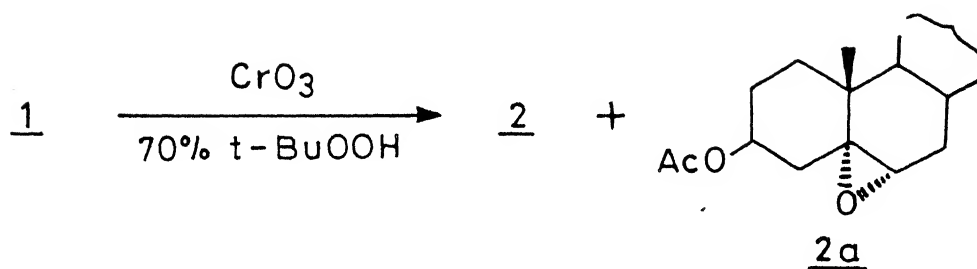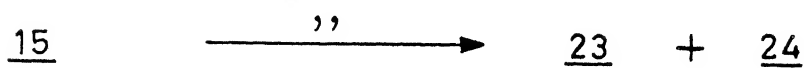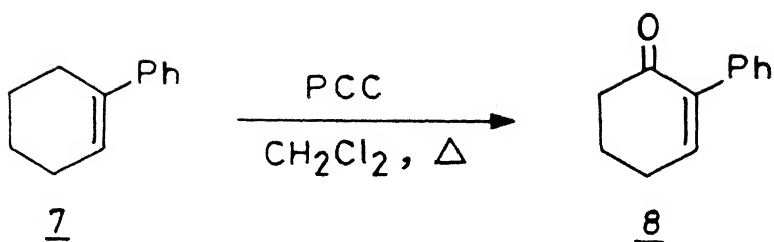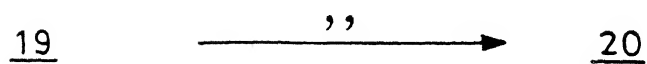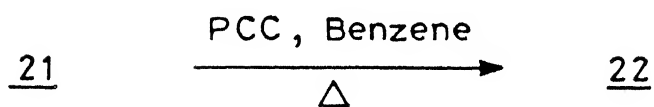
Ditertiarybutyl chromate has earlier been used for allylic oxidation successfully. It was anticipated that if the corresponding t-butyl peroxy chromate ester is formed _in situ_ in the reaction, it might turn out to be a superior reagent for allylic and benzylic oxidations. Studies related to the development and use of such a reagent for oxidative transformations are reported in this chapter.

I.1.b Results and Discussion
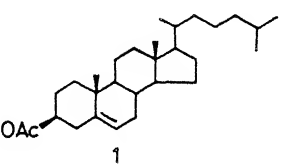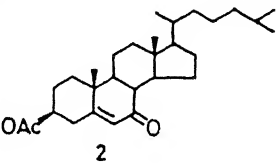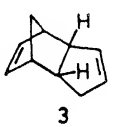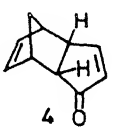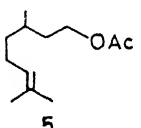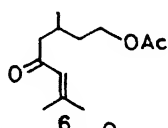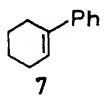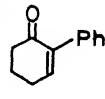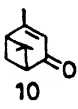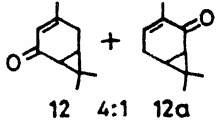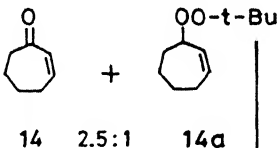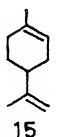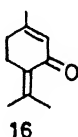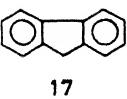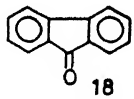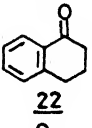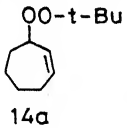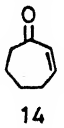
Generally pyridinium dichromate or t-butyl hydroperoxide independently are not known to effect allylic and benzylic oxidations. It was believed that if they are allowed to react a peroxy chromate ester **A** may be formed _in situ_ which would be useful as an oxidising agent.

$$\text{>-0-0-H} + (C_5H_5NH)_2Cr_2O_7 \quad \text{------->} \quad \text{->-0-0-}\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{C}}}}\text{r-0}^- \; C_5H_5\overset{+}{N}H$$
$$\underline{\mathbf{A}}$$
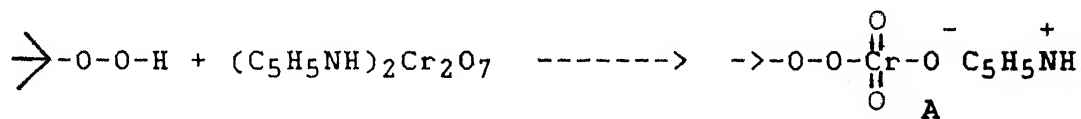
Accordingly pyridinium dichromate (1 eq) in benzene at $10^{\circ}C$ was treated with t-butyl hydroperoxide (1 eq.) for 5 min. A clear orange red solution was formed, which was subsequently used for oxidation for a variety of substrates. It turns out that such a combination of pyridinium dichromate/t-butyl hydroperoxide (1:1) is a very good reagent system for carrying out allylic and benzylic oxidations under very mild conditions. A number of examples of successful oxidations are presented in Table 1. A. 1. The experiments were generally carried out in dry benzene at $25^{\circ}C$ containing 2 eq. of t-butyl hydroperoxide and 2 eq. of pyridinium

TABLE I.A.1

Entry	Substrate	Substrate: t-BuOOH:PDC	Reaction time, h	Product	Conversion,%	Yield,%
1	1	1:4:4	4	2	84	81
2	3	1:2:2	7	4	74	44
3	5	1:2:2	11	6	69	40
4	7	1:2:2	9	8	60	30
5	9	1:2:2	9	10	64	37
6	11	1:2:2	9	12 4:1 12a	55	29
7	13	1:3:3	9	14 2.5:1 14a	57	58
8	15	1:2:2	9	16	48	23
9	17	1:4:4	14	18	90	99.5
10	PhCH₂Ph 19	1:4:4	14	PhC(O)Ph 20	77	76
11	21	1:2.5:2.5	6.5	22	82	78
12	14a	1:2:2	2	14	100	90

dichromate. In order to put the present results in the right perspective, they have to be compared with some of the other methods for effecting the same transformations. For example, 2 was obtained from cholesteryl acetate with collin's reagent (yield 74%)[9], by heating t-butyl hydroperoxide and highly toxic chromium hexacarbonyl catalyst (yield 80%)[2] or by using 7 eq. of 70% t-butyl hydroperoxide and catalytic amount of chromium trioxide to give the enone 2 (yield 44%) and epoxy compound 2a (yield 20%)[5], whereas the present method affords only 2 (81%) in a very short time.

In a typical example of benzylic oxidation, tetralone 22 was obtained from tetralin 21 with 5 eq. of chromium trioxide in acetic acid/acetone (yield 55%)[10], 15 eq. of bipyridinium chloro chromate (yield 63%)[11], 7 eq. of 70% t-butyl hydroperoxide and a catalytic amount of chromium trioxide to give 22 (yield 64%) and 1,4-naphthoquinone 22a (yield 5%)[4], whereas our method (yield 78%, 6.5 h) is far superior. This oxidation requires a reagent ratio (1:2.5:2.5). We have observed that higher reagent ratio which was generally used for benzylic oxidations (1:4:4) and long reaction times (14 h) give inferior yields. Fluorene 17 with 7 eq. of anhydrous t-butyl hydroperoxide and chromium hexacarbonyl catalyst gives 18 (yield 57%) and t-butyl peroxyfluorene (yield 39%)[3], with 7 eq. of 70% t-butyl hydroperoxide and catalytic amount of chromium trioxide gives 18 (yield 95%) whereas our method affords 18 (yield 99.5%, 14 h).

An interesting feature in the allylic oxidation using the present methodology is exemplified in the oxidation of limonene **15** and 1-phenylcyclohexene **7**, where high regioselectivity is observed. Many of the existing methods of allylic oxidation of limonene give a mixture of carvone and isopiperitenone as major products of the reaction, whereas with present methodology piperitenone **16** (23%) was the only product formed. 1-Phenylcyclohexene **7** gave exclusively 2-phenyl-2-cyclohexenone **8**[16] (30%).

In the case of allylic oxidation of cycloheptene **13**, apart from the enone **14** (41%), the t-butyl peroxy compound **14a** (17%) was also isolated. The peroxy derivative was not formed if pyridinium dichromate was not used in the reaction. Similar observations on the formation of peroxy compounds in benzylic oxidations have been reported by Muzart recently.[3] The peroxy compound **14a** on treatment with t-butyl hydroperoxide/pyridinium dichromate gave rise to **14** indicating that compounds of this type are potential intermediates in the pathway leading to the enones. Compound **14a** on reduction with lithium aluminium hydride yielded cycloheptenol.

Allylic oxidations in general are proposed to proceed by abstraction of an hydrogen atom (or hydride) from the allylic carbon to give an allylic radical (or carbonium ion). The resulting species is then oxidized at either terminal end of allylic radical (or ion) to yield an α,β-unsaturated ketone.[9,12]
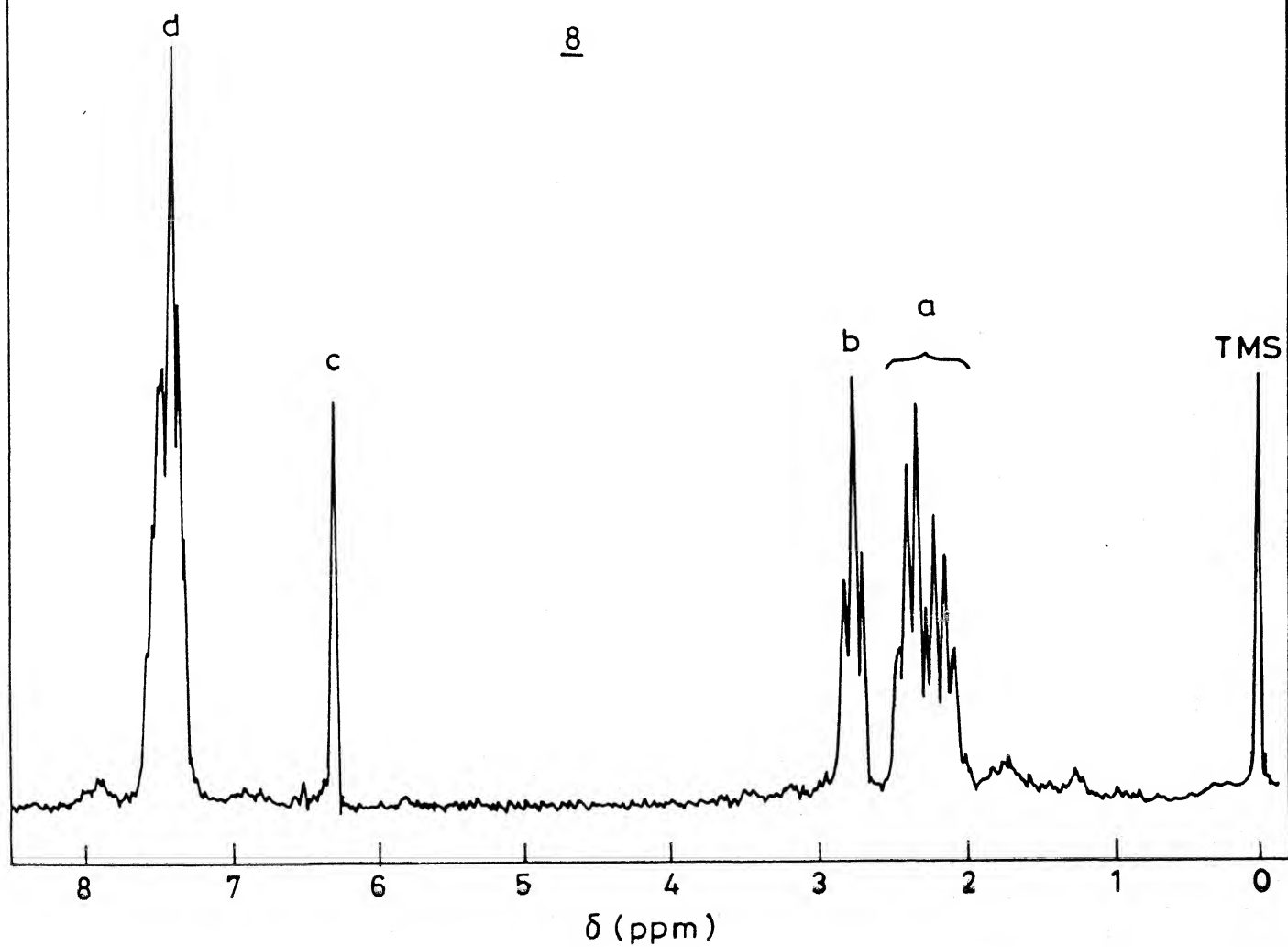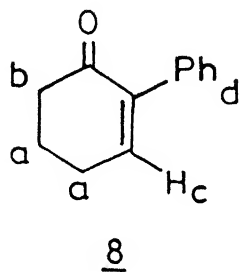
^{1}H NMR spectrum (90 MHz) of 8 .

^{1}H NMR spectrum (90 MHz) of 16 .

$$R-CH_2-CH=CH-R' \xrightarrow[Cr(VI)]{-H\cdot} R-\overset{\cdot}{\overline{CH-CH-CH}}-R' + Cr(V)$$

$$\downarrow Cr(VI)/Cr(V)$$

$$R-\overset{O}{\overset{\|}{C}}-CH=CH-R' + R-CH=CH-\overset{O}{\overset{\|}{C}}-R'$$
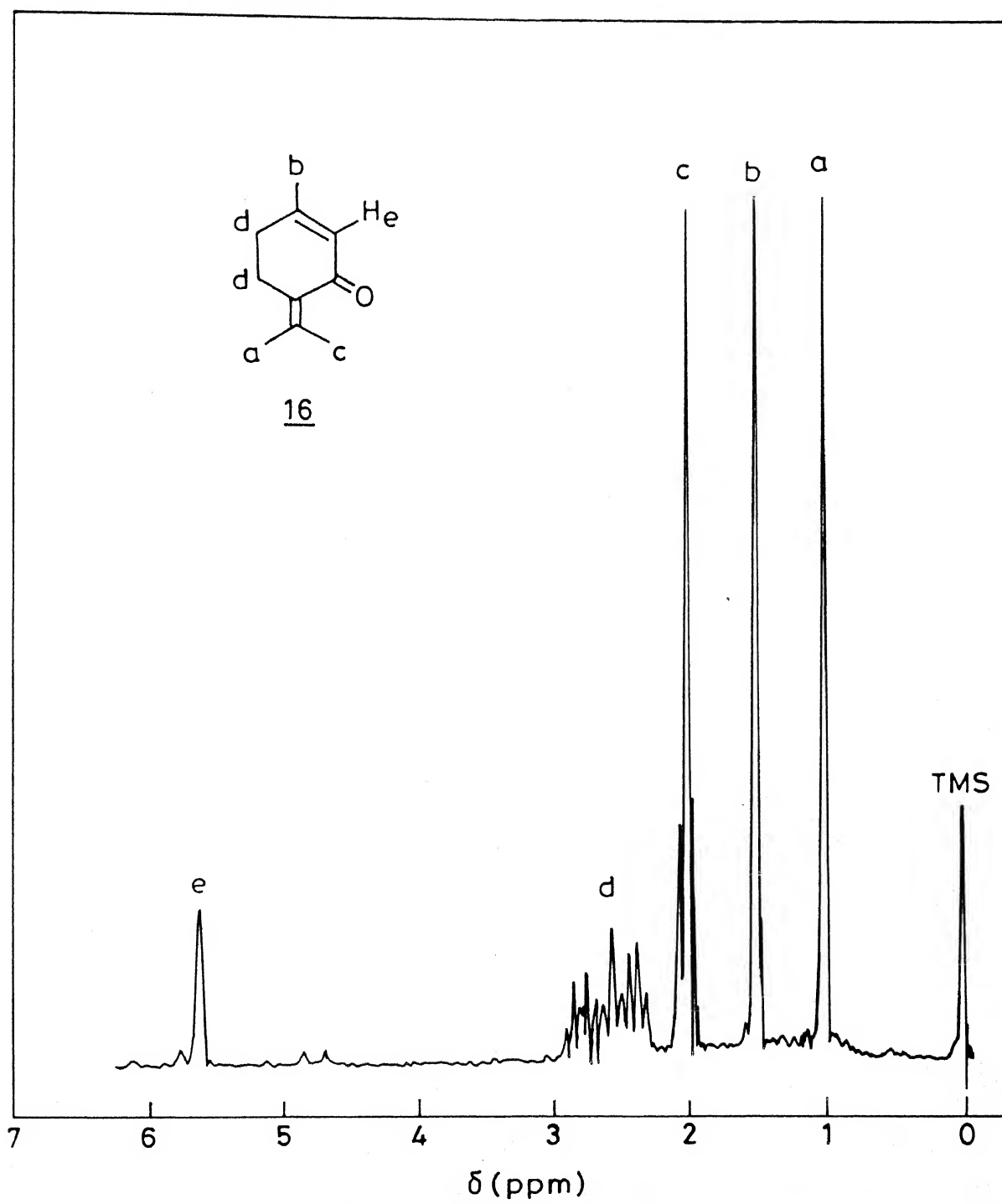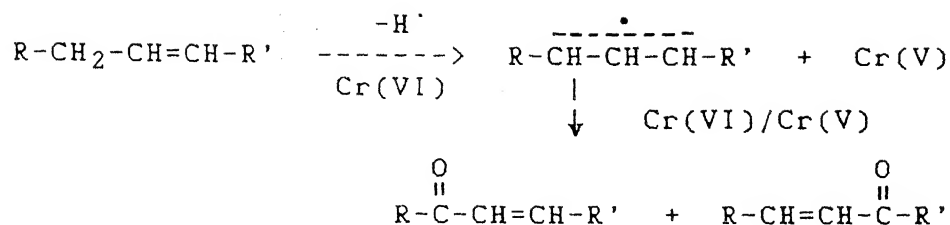
With the present reagent system it is likely that the actual oxidising agent is the tertiary butyl peroxy chromate ester **A**.
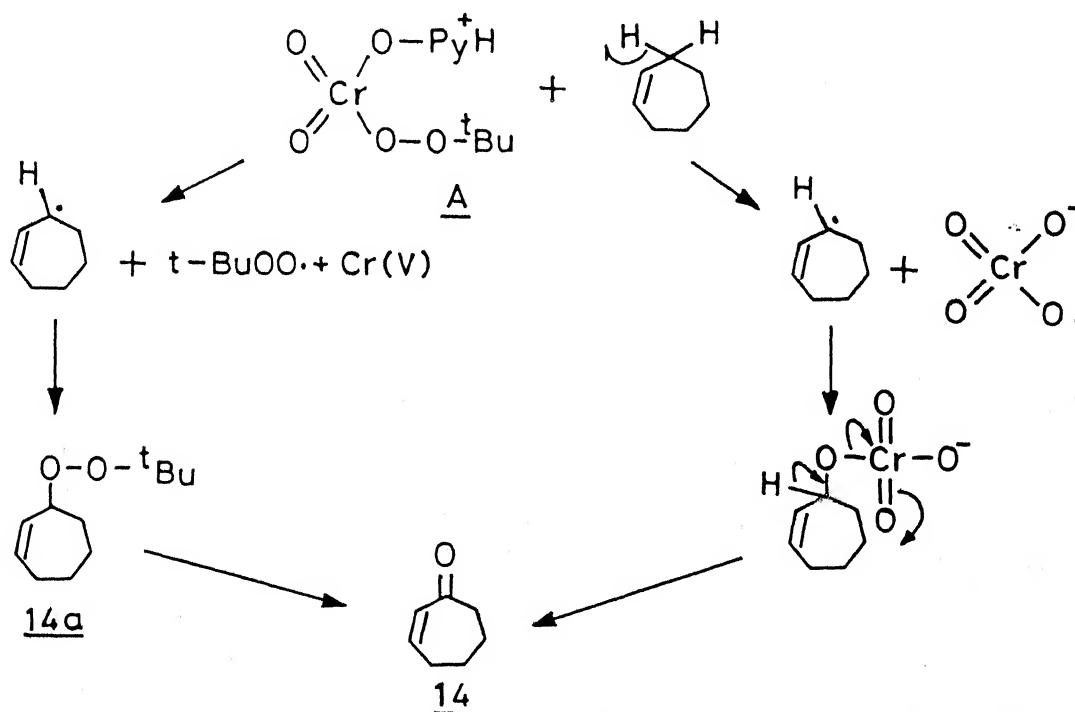
As a peroxy chromium(VI) species it tends to undergo reaction by radical process involving single electron transfer to produce allylic radical B which can then form the chromate ester and decompose to give the α,β-unsaturated ketone **14**. This pathway may also explain the formation of t-butyl peroxy compound **14a** which is formed as a by product in some allylic oxidations.

Recently, Firouzabadi[22] reported the use of chromoium peroxo complexes in the oxidation of alcohols to carbonyl compounds.

Another interesting feature about this (PDC / t-BuOOH) reagent is that it does not readily oxidise primary and secondary alcohols unlike other chromium(VI) reagents. For example 2-octanol and 1-octanol on treatment with this reagent for 3 h under normal reaction conditions gave rise to the corresponding carbonyl compounds only to the extent of about 10 - 15%. Most of the starting alcohols were recovered unchanged. This chemoselectivity of the present methodology can be taken advantage of, in practical organic synthesis.

I.1.c Experimental

General Procedures

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, tlc, m.p.).

Materials

Commercial grade solvents were distilled prior to use. Benzene was distilled after storing over calcium chloride and kept over sodium wire. Pyridine was distilled over potassium hydroxide pellets. Chromium trioxide flakes (BDH, E. Merck) and 70% t-butyl hydroperoxide (Koch Light Laboratories Ltd.) were

used as such. Petroleum ether fractions 60-80°C were used for chromatography. Cholesteryl acetate, citronellol acetate and 1-phenyl cyclohexene were prepared by known methods.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) Ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200°C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and then reimmersion and heating to ca. 200°C.

Column chromatography was performed using 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical data

Melting points (m.p.) were determined with a Uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80 instrument. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), etc. Coupling constants are reported wherever necessary and are expressed in Hz. Mass spectra (MS) were recorded on a Jeol JMS-D 300 mass spectrometer. Principal molecular fragments are reported.

Preparation of pyridinium dichromate[24]

Pyridine (78.83 g, 0.996 mol, 80.6 mL) was gradually added to a cooled solution of chromium trioxide (100 g, 1 mol) in water (100 mL) at <30°C. The solution was diluted with acetone (400 mL) and cooled to -20°C to yield orange crystals. The product was collected over a Buchner funnel, washed with cold acetone and dried in vacuo, to give pyridinium dichromate (120 g, 0.319 mol) in 64% yield.

m.p. : 144-146°C (lit.[24] m.p. 144-146 °C).

Oxidation of cholesteryl acetate 1

To a stirred solution of cholesteryl acetate 1 (0.430 g, 1 mmol) in benzene (12 mL) and Celite (1.2 g) was added pyridinium dichromate (1.5 g, 4 mmol) followed by the addition of 70% tert-butyl hydroperoxide (0.360 g, 4 mmol) at 10°C. After 15 min at 10°C, the reaction mixture was stirred for 4 h at 25°C. Ether

(30 mL) was added, and the reaction mixture was filtered through a pad of Celite and washed twice with 20 mL portions of ether. The combined filtrate was evaporated and the residue was purified by flash chromatography (10% ethyl acetate in petroleum ether to afford unreacted starting material (0.069 g, 16%) and the enone **2** (0.279 g, 81%) as a white solid.

m.p.	: 152-153°C (lit.[2,13] m.p. 155-156°C)
IR (KBr)	: 1730, 1670 cm^{-1}.
^{1}H NMR (CCl$_4$)	: 1.95 (s, 3H), 2.47 (br, 2H), 4.5 (m, 1H) 5.57 (s, 1H).

Oxidation of dicyclopentadiene 3

Compound **3** (0.413 g, 3.1 mmol) in benzene (12 mL) and Celite (2.5 g), pyridinium dichromate (2.35 g, 6.2 mmol), and tert-butyl hydroperoxide (0.563 g, 6.2 mmol, 0.6 mL) were treated as above (7 h). Flash chromatography afforded unreacted starting material (0.110 g) and the enone **4** (0.146 g, 44% based on starting material consumed) as a colorless solid.

m.p.	: 75-77°C (lit.[14,15] m.p. 77-79°C).

Oxidation of citronellol acetate 5

Compound **5** (0.401 g, 2 mmol) under similar conditions yielded the enone **6** (0.172 g, 40%) as an oil.

IR (thin film)	: 1730, 1680 cm^{-1}.
^{1}H NMR (CCl$_4$)	: 0.9 (d, 3H), 1.95 (s, 3H), 4.0 (t, 2H), 5.95 (s, 1H).
MS (m/e)	: 212 (M$^+$).

Oxidation of 1-phenylcyclohexene 7

Compound 7 (0.625 g, 3.95 mmol) in benzene (25 mL) and Celite (2.97 g), PDC (2.97 g, 7.9 mmol), and t-butylhydroperoxide (0.71 g, 7.9 mmol) under similar reaction conditions gave after chromatography unreacted starting material (0.26 g) and enone 8 (0.120 g, 30%).

m.p.   : 94-95°C (lit.[16] m.p. 95-96°C).

IR (KBr)   : 1660, 1600 cm^{-1}.

^{1}H NMR (CCl_4)   : 2.0-2.5 (m, 4H), 2.72 (t, 2H), 6.28 (s, 1H)
                         7.40 (m, 5H).

Oxidation of α-pinene 9

Compound 9 (0.270 g, 1.98 mmol) under similar reaction conditions afforded after chromatography verbenone 10 (0.109 g, 37%).[17,18]

IR (neat)   : 3040, 2940, 2870, 1665, 1615 cm^{-1}.

^{1}H NMR (CCl_4)   : 0.93 (s, 3H), 1.43 (s, 3H), 1.93 (s, 3H)
                         2.15-2.85 (m, 4H), 5.58 (s, 1H).

Oxidation of Δ^3-carene 11

Compound 11 (0.527 g, 3.87 mmol) under similar reaction conditions afforded after chromatography car-3-en-2-one 12a (0.036 g, 6.2%) and car-3-en-5-one 12 (0.130 g, 22.4%). The spectral data for car-3-en-2-one 12a[19,20] are as follows :

IR ($CHCl_3$)   : 3010, 2920, 1665, 1620 cm^{-1}.

^{1}H NMR (CCl_4)   : 1.33 (s, 3H), 1.37 (s, 3H), 1.52 (s, 2H) 1.95
                         (br s, 3H), 2.2 (br s, 2H), 6.43 (br s, 1H).

The spectral data for car-3-en-5-one $\underline{12}$[19] are as follows :

IR (neat)   : 3010, 2960, 1660 cm^{-1}.

^{1}H NMR (CCl$_4$)   : 1.03 (s, 3H), 1.2 (s, 3H), 1.4 (s, 2H)

1.87 (s, 3H), 2.5 (m, 2H), 5.7 (s, 1H).

Oxidation of cycloheptene $\underline{13}$

Cycloheptene $\underline{13}$ (0.288 g, 3 mmol) under the same conditions of oxidation gave the enone $\underline{14}$ (0.151 g, 46%; identical with an authentic sample) and the peroxy compound $\underline{14a}$ (0.063 g, 12%) as an oil. The spectral data for $\underline{14a}$ are as follows :

IR (thin film) : 1198, 788, 760 cm^{-1}.

NMR (CDCl$_3$)   : 1.2 (s, 9H), 5.7 (s, 1H).

MS (m/e)   : 95 (C$_7$H$_{11}$)$^+$, 73 (C$_4$H$_9$O)$^+$, 57 (C$_4$H$_9$)$^+$.

The spectral data for $\underline{14}$[21] are as follows :

IR (thin film) : 3020, 2920, 1670 cm^{-1}.

NMR (CCl$_4$)   : 2.5 (br s, 4H), 5.93 (d, 1H, J=12Hz),

6.47 (dt, 1H).

Reduction of $\underline{14a}$ with lithium aluminium hydride

Compound $\underline{14a}$ (0.020 g) on treatment with lithium aluminium hydride (0.025 g) in THF (3 mL) under reflux for 4 h gave cyclo-heptenol (0.012 g), found to be identical with an authentic sample.

Oxidation of limonene 15

15 (0.525 g, 3.8 mmol) on oxidation under conditions described earlier gave after chromatography the enone 16 (0.130 g 23%) as an oil:

IR (CHCl$_3$)   : 1670, 1615 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.02 (s, 3H), 1.55 (s, 3H), 2.0 (s, 3H),

2.3-2.9 (m, 4H), 5.65 (m, 1H).

MS (m/e)   : 150 (M$^+$).

Oxidation of fluorene 17

17 (0.347 g, 2.1 mmol) under the same conditions of oxidation and after the usual workup yielded the unreacted starting material (0.030 g) and fluorenone 18 (0.342 g, 99.5%) as a yellow solid.

m.p.   : 80-81°C.

Oxidation of diphenylmethane 19

19 (0.332 g, 2.1 mmol) under the same conditions yielded after chromatography, unreacted starting material (0.076 g) and benzophenone 20 (0.211 g, 76%).

m.p.   : 49-50°C.

Oxidation of tetralin 21

Tetralin 21 (0.311 g, 2.35 mmol) under similar conditions of oxidation afforded the unreacted starting material (0.010 g) and -tetralone 22 (0.26 g, 78%).

b.p.   : 113-116°C/6mm (lit[23] 129°C/12mm).

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OXIDATION OF ENOL ETHERS WITH PDC/t-BuOOH

I.2   Introduction

I.2.a Oxidation of enol ethers to α,β-unsaturated lactones

Oxidation of enol ethers to esters, γ and δ-lactones, keto-lactones using Cr(VI) reagents such as CrO_3, pyridinium chloro-chromate (PCC) are known in the literature.[1,2]

Oxidation of cyclic enol ethers to α,β-unsaturated lactones has been achieved using singlet oxygen. Dihydropyran 1 on treat-ment with [1]O_2 gives dihydro-2-pyrone 3.[3,4] This has also been achieved by various other methods.[5-7] The methodology utilising singlet oxygen is not generally applicable for large scale mani-pulation and they have to be done in high dilution. Short and efficient synthesis of dihydro-2-pyrone 3 is important because it is a precursor for 2-pyrone 4[7-9], which is the basic skeleton present in flavanoids. It is also an effective butadiene equi-valent, since 2-pyrone 4 is a liquid which is stable and can be handled easily compared to butadiene. Industrially 2-pyrone is prepared from coumalic acid 5 under flash vacuum pyrolysis conditions.[10b]

α,β-unsaturated-δ-lactones occur in several food flavours and essential oils as metabolites of high molecular weight un-saturated fatty acids. They are used for controlling the diff-erential growth of animal tissues and also as an abortifacient. Some of them, which have been isolated and studied recently are

argentilactone (6-(Z)-2,6-dodecadien-5-olide)[11-14] **25**, gonio-thalamin[13,15-19] [(E)-6-(2-phenylvinyl)5,6-dihydro-2H-pyran-2-one] **27**, and goniothalaminoxide **28**.

Dihydro-2-pyrone **3** has been synthesized in 37% yield by refluxing a mixture of vinyl acetic acid **35**, paraformaldehyde **36** and conc. sulfuric acid in acetic acid (Scheme I. B. 1). Dihydro-2-pyrone **3** so obtained is brominated by using N-bromosuccinamide and benzoylperoxide in carbon tetrachloride to give 5-bromo-5,6-dihydro-2-pyrone **3a**, which on refluxing with triethylamine yields 2-pyrone **4**[7].

Argentilactone **25** a constituent of the rhizomes of aristolochia argentina was isolated and characterized recently.[11] A few syntheses of this compound have been reported in the literature.[12-14] The first synthesis of argentilactone **25** was achieved in 60% yield by treatment of 2-[(Z)-1-heptenyl]-3,4-dihydro-2H-pyran **23** with one equivalent of singlet oxygen followed by triethylamine and acetic anhydride[12] (Scheme I. B. 2) Compound **23** was prepared by a Wittig reaction with 3,4-dihydro-pyran-2-carboxaldehyde **22**. Thus, to the ylid generated in situ from hexyltriphenylphosphonium bromide and sodium hydride in dimethyl sulfoxide was added **22** to give **23** in 71% yield. Recently two chiral syntheses of argentilactone **25** have also been reported[13,14] (Scheme I. B. 3 and I. B. 4).

Goniothalamin **27** a constituent of species goniothalamus macrophyllus has attracted considerable attention recently and the isolation, structural elucidation[15,16,18] and synthesis[13,17,19]

SCHEME I.B.1[7]

35 + HCHO **36** →(H⊕)→ **3** + CH₃COOCH₂CH₂...COOH

$$\underline{35} \quad + \quad HCHO \xrightarrow{H^{\oplus}} \quad \underline{3} \quad + \quad CH_3COOCH_2CH_2$$

3 → **3a** → **4**

SCHEME I.B.2[12]

22 → **23** →($^1O_2$, TEA/Ac₂O)→ **25**

SCHEME I.B.3[13]

R = CH = CH₂
 = CH₂CO₂Me

X = O
 = (Z) CH(CH₂)₄CH₃
 = CHPh
 = (E)- CHPh

27

X = (Z)-CH(CH₂)₄CH₃
 (E)-CHPh

25

SCHEME I.B.4[14]

25
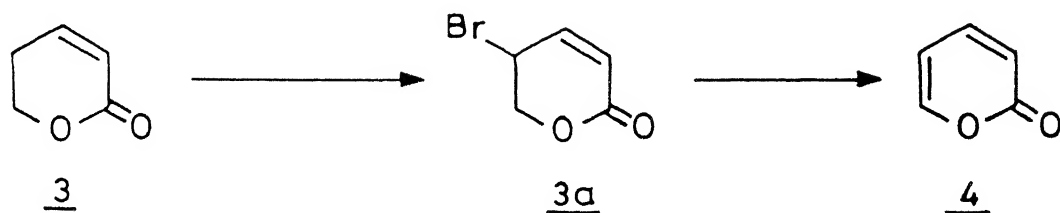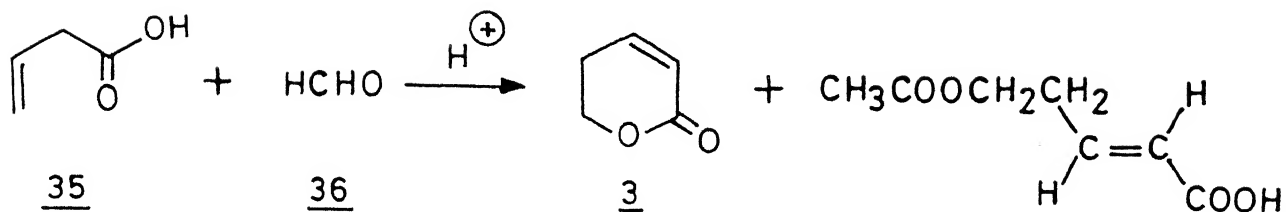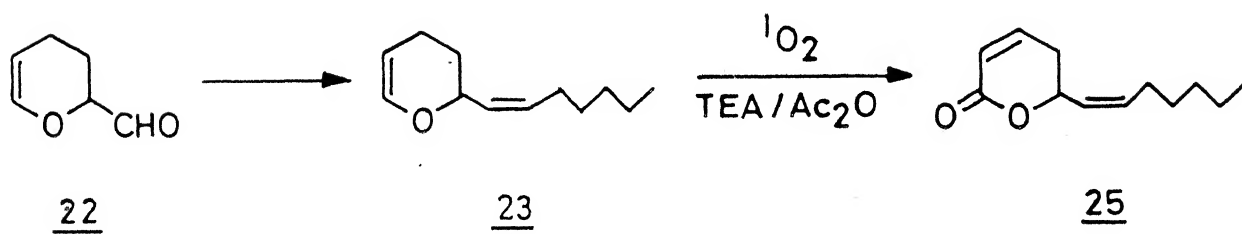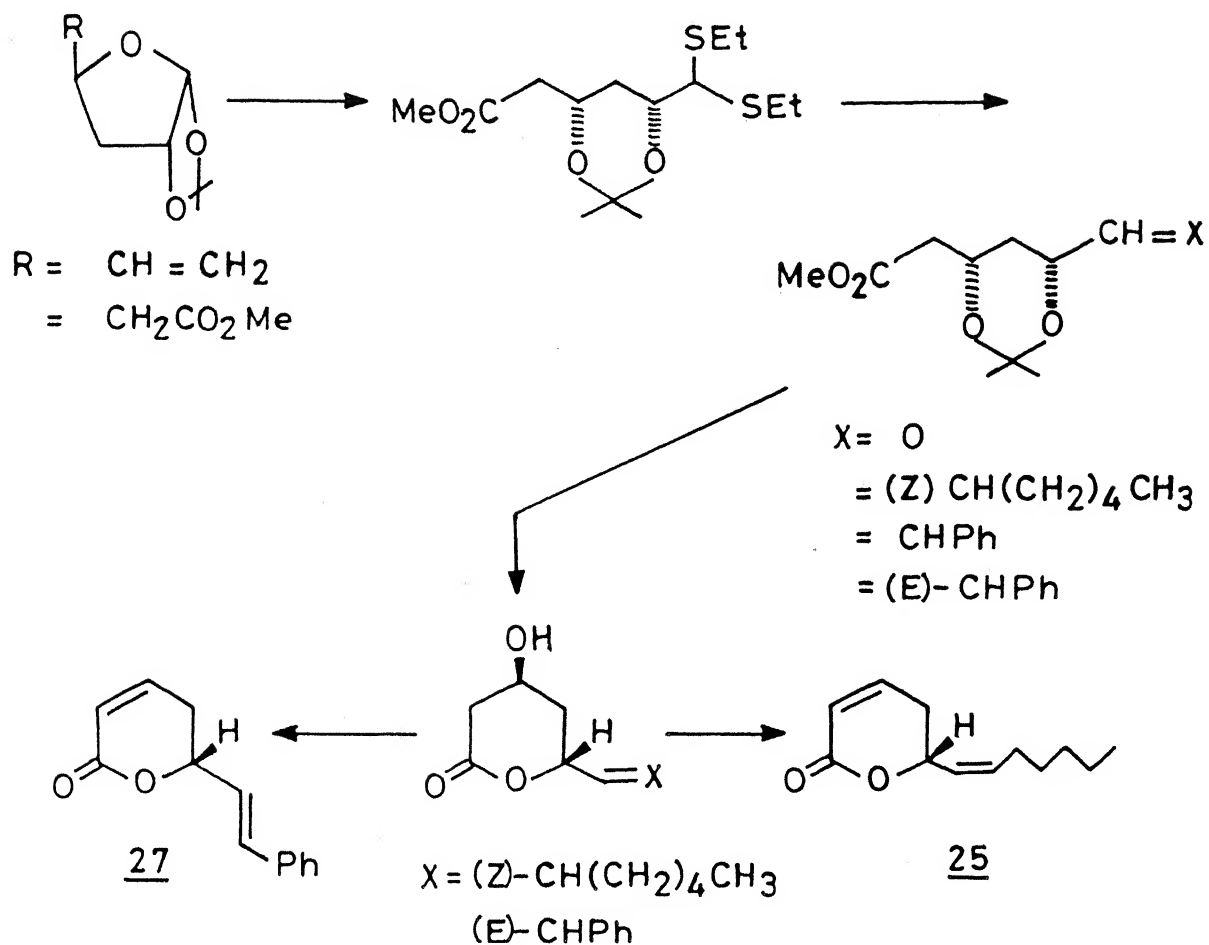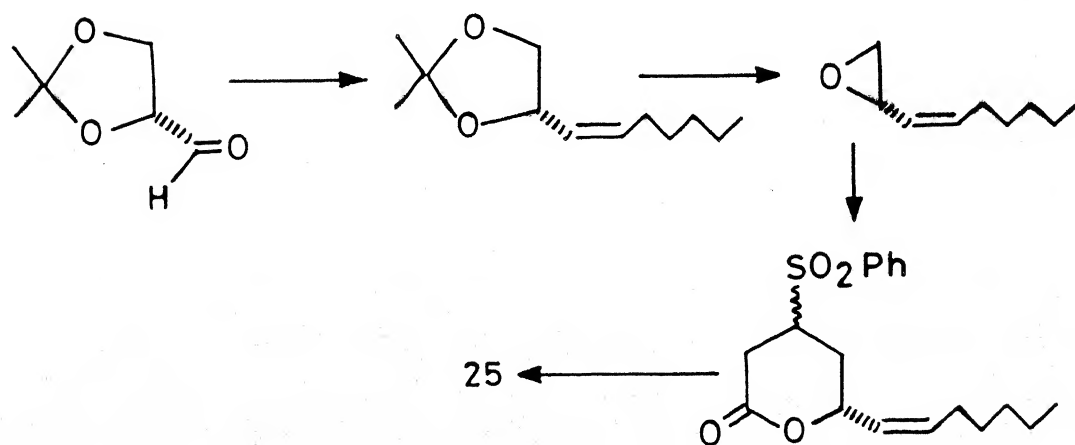
(Scheme I. B. 3) have been reported. The epoxide of goniothalamin 27 known as goniothalamin oxide 28 is an embryotoxic compound.

Our interest on the synthesis of these compounds arose from our results on the oxidation of dihydropyran 1 with pyridinium dichromate/t-butyl hydroperoxide to get 5,6-dihydro-2-pyrone 3 and to extend the applicability of this novel oxidative re-arrangement methodology for the synthesis of these naturally occuring compounds.

I.2.b Results and Discussion

Pyridinium dichromate/t-butyl hydroperoxide when mixed in a 1:1 molar ratio turns out to be an excellent reagent for allylic and benzylic oxidations (Chapter I.1). Reactivity of Cr(VI) reagents like chromium trioxide and pyridinium chlorochromate towards cyclic and acyclic enol ethers is well known[2].

Piancatelli and co-workers[2a] have observed that ethyl vinyl ether 31 on treatment with Cr(VI) reagent pyridinium chloro-chromate gives ethyl acetate in 75% yield. Similarly dihydro-pyran 1 gives δ-valerolactone 32 in 90% yield and dihydrofuran 33 gives γ-butyrolactone 34 in 85% yield (Scheme I. B .5).

A recent report from our laboratory[2b] has shown that substi-tuted bicyclic enol ethers on treatment with pyridinium chloro-chromate give macrocyclic ketolactones in yields ranging from 63-85% (Scheme I. B. 6).

SCHEME I.B.5[2a]

31 →

1 → **32**

33 → **34**
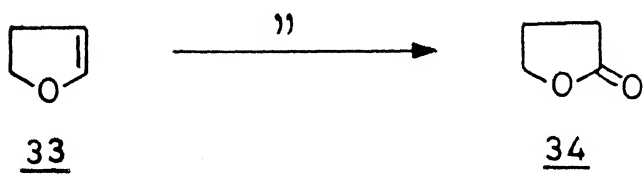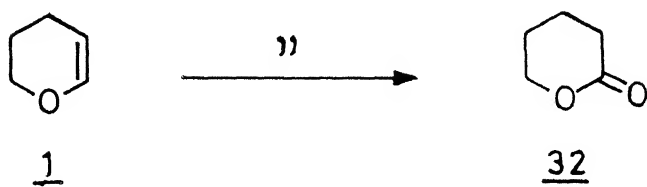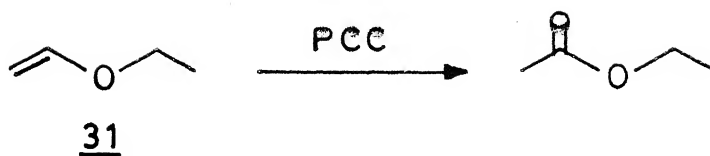
SCHEME I.B.6[2b]
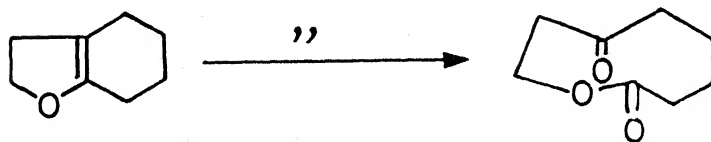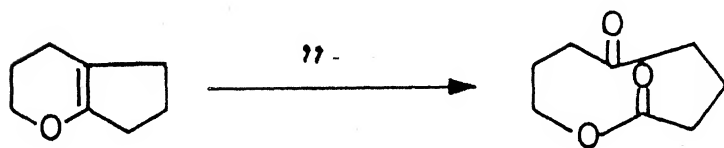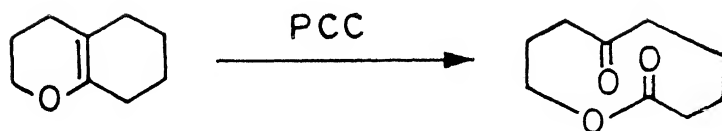
Hence, it was of interest to study the reactivity of this new Cr(VI) reagent, (PDC/t-BuOOH) with cyclic and acyclic enol ethers with a view to find out whether a simple allylic oxidation or oxidation with rearrangement would take place.

In the study of oxidation of enol ethers, initially pyridinium dichromate was allowed to react with t-butyl hydroperoxide (2:3) in dichloromethane at 0°C and the orange red solution thus obtained was filtered over a cotton plug and used subsequently. This modified procedure was found to be superior to the one used in the allylic oxidations where the reagent was generated in situ. Treatment of dihydropyran 1 with the oxidant generated from PDC/t-BuOOH (2:3) at 0°C for 2 h gave dihydro-2-pyrone 3 as the major product in 50% yield. The isomeric dihydro-4-pyrone 3b was not detected in the reaction mixture. However a small amount (6%) of the t-butyl peroxy compound 2 was also obtained. This peroxy compound on treatment with an equivalent of triethylamine in toluene at 80°C (1 h) got converted to the dihydro-2-pyrone 3. Thus the total yield of dihydro-2-pyrone 3 in this reaction was 55% .

5,6-Indenyldihydro-2H-pyran 7 was prepared in 40% yield by hetero Diels-Alder reaction of indene 6 and acrolein.[20] Reaction of 7 with the oxidant at 0°C prepared by the modified method yielded the t-butyl peroxy compound 8 and the α,β-unsaturated lactone 9 in 38% and 43% yield respectively. Reaction of 8 with triethylamine in toluene at 80°C for 0.5 h, resulted in complete
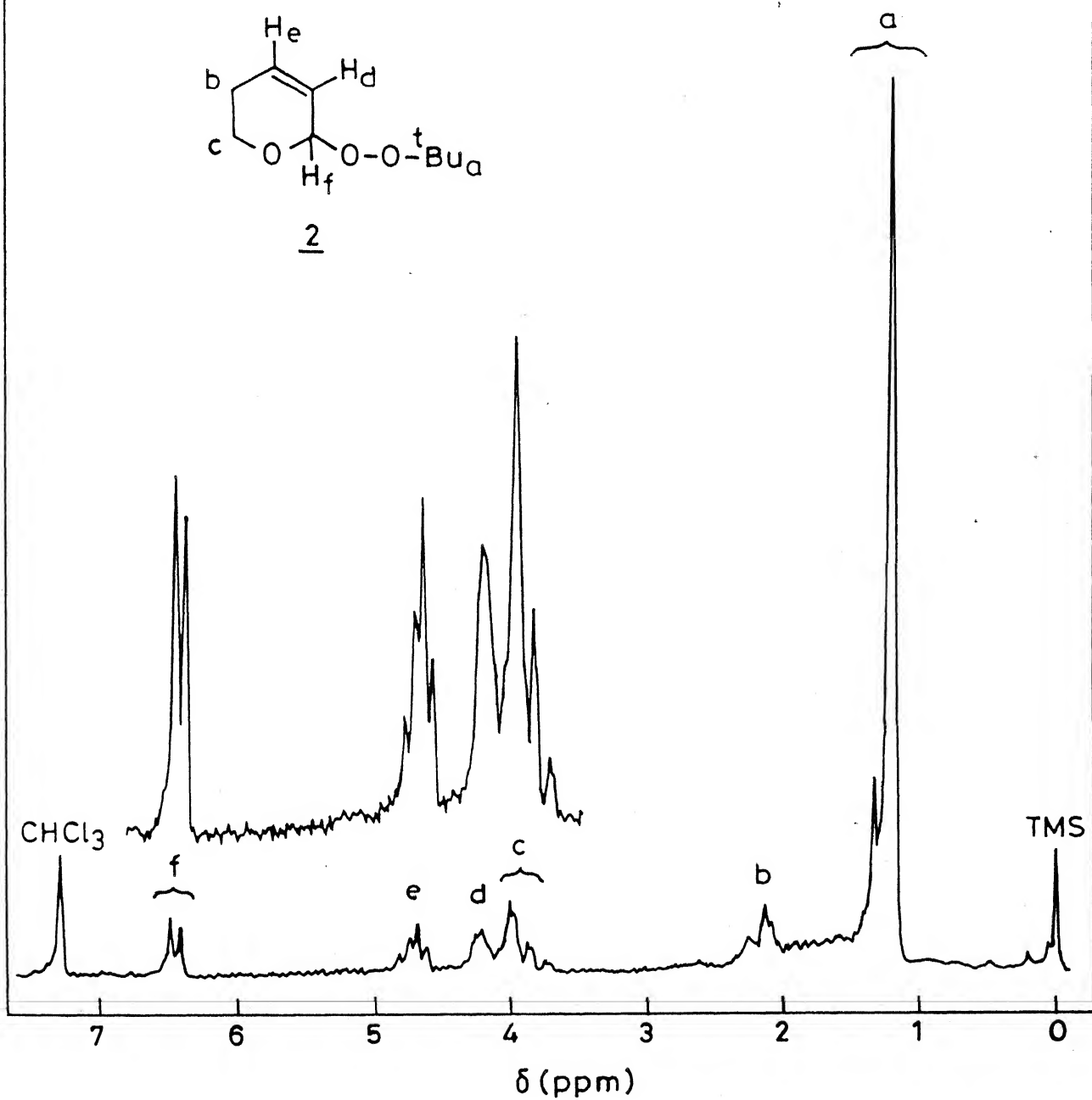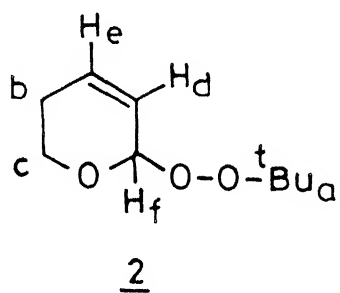
^{1}H NMR spectrum (90 MHz) of 2 .
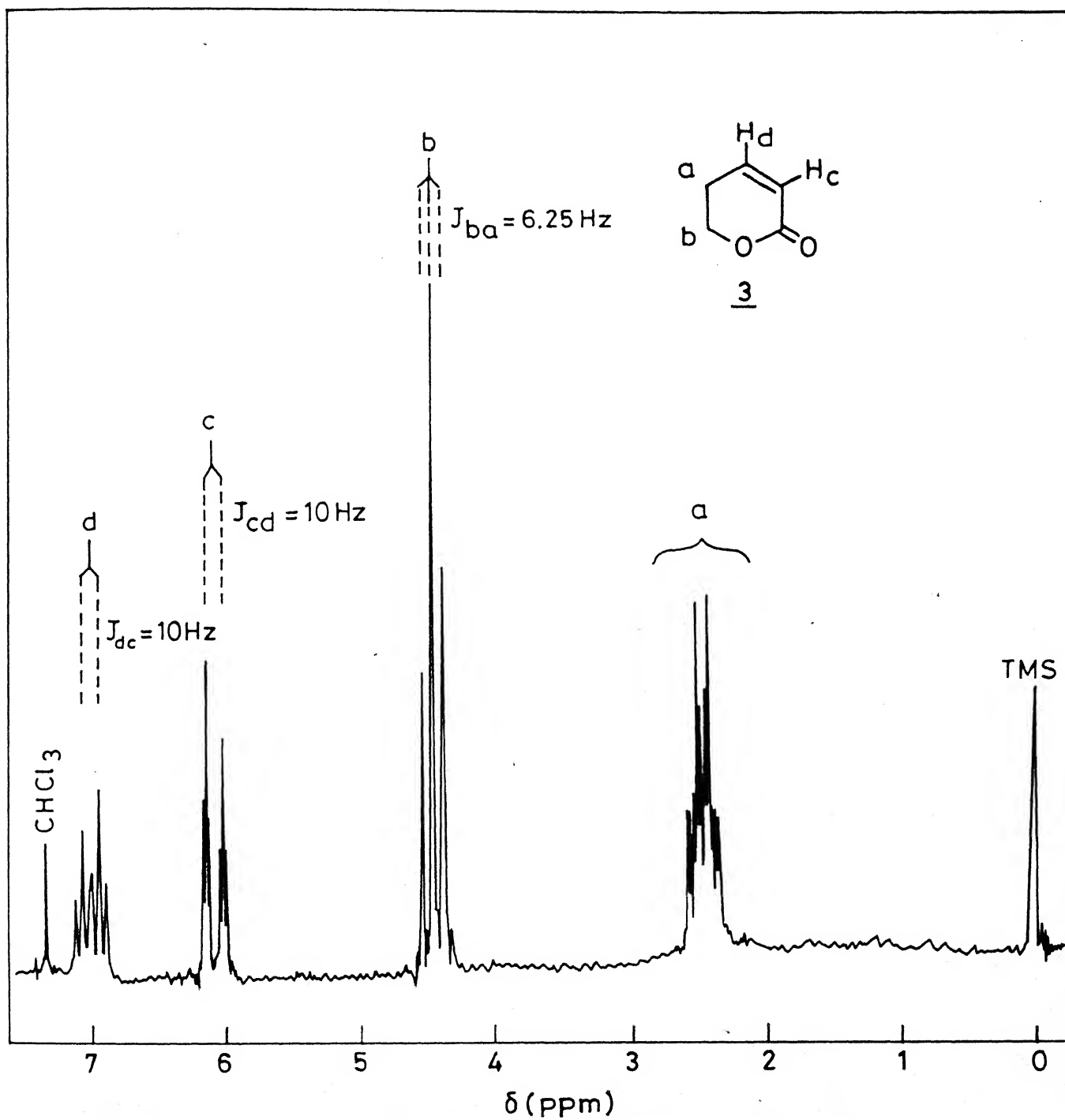
^{1}H NMR spectrum (80 MHz) of 3 .

conversion to the lactone 9 raising the total yield of 9 to 70% (Scheme I. B. 7).

Similarly the exo-tricyclic enol ether 29[29] was synthesized by [4+2] cycloaddition of norbornene and acrolein in 54% yield which on oxidation with PDC/t-BuOOH at 0°C for 3 h yielded a mixture of unsaturated lactone 30 in 42% yield and the t-butyl peroxy compound 30a in 18% yield. This peroxy compound 30a could also be converted to the lactone 30 on treatment with triethyl-amine in toluene at 80°C for 0.5 h increasing the yield of the lactone 30 to 52% (Scheme I. B. 7).

In order to test the scope of this novel oxidative rearran-gement reaction, the spiro enol ether 13[21] was prepared. This could be obtained easily by Diels-Alder reaction of acrolein with tetrahydro-2-methylene furan 12[21, 22] (Scheme I. B. 8). Enol ether 13 was subjected to the same oxidation conditions with PDC/t-BuOOH at 0°C for 4 h, to afford 2-(2-hydroxyethyl)cyclohex-2-enone 14 in 50% yield. The structure of the product was corro-borated by the spectral and analytical data on compound 14 as well as its acetate 15. This product 14 obviously arises not by oxidation but by acid catalysed hydrolysis of the spiro enol ether which then undergoes an intramolecular aldol reaction (Scheme I. B. 8). Addition of propylene oxide as acid scavenger in this reaction along with the oxidant was not found to be effective.

SCHEME I.B.7
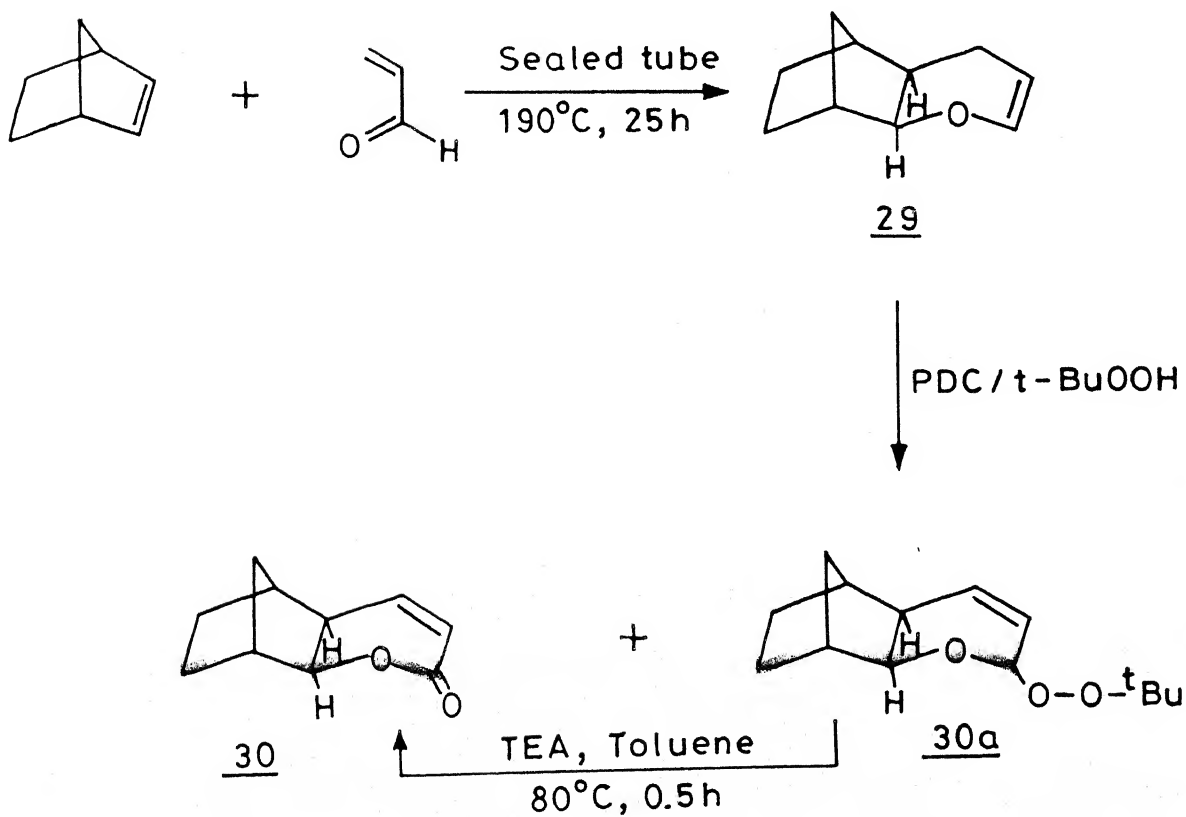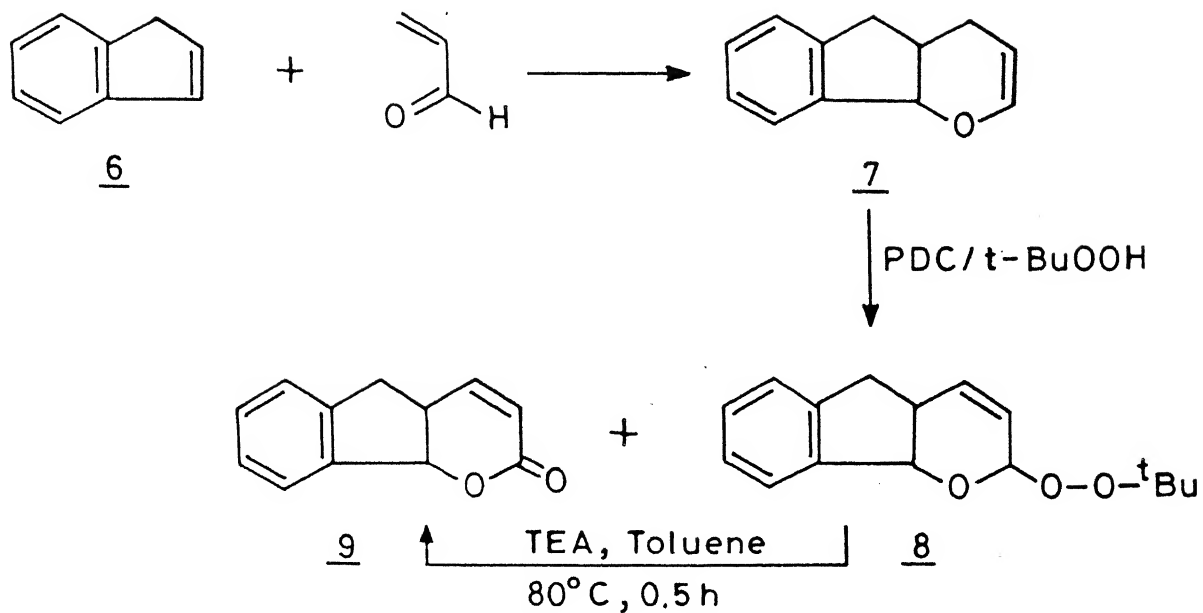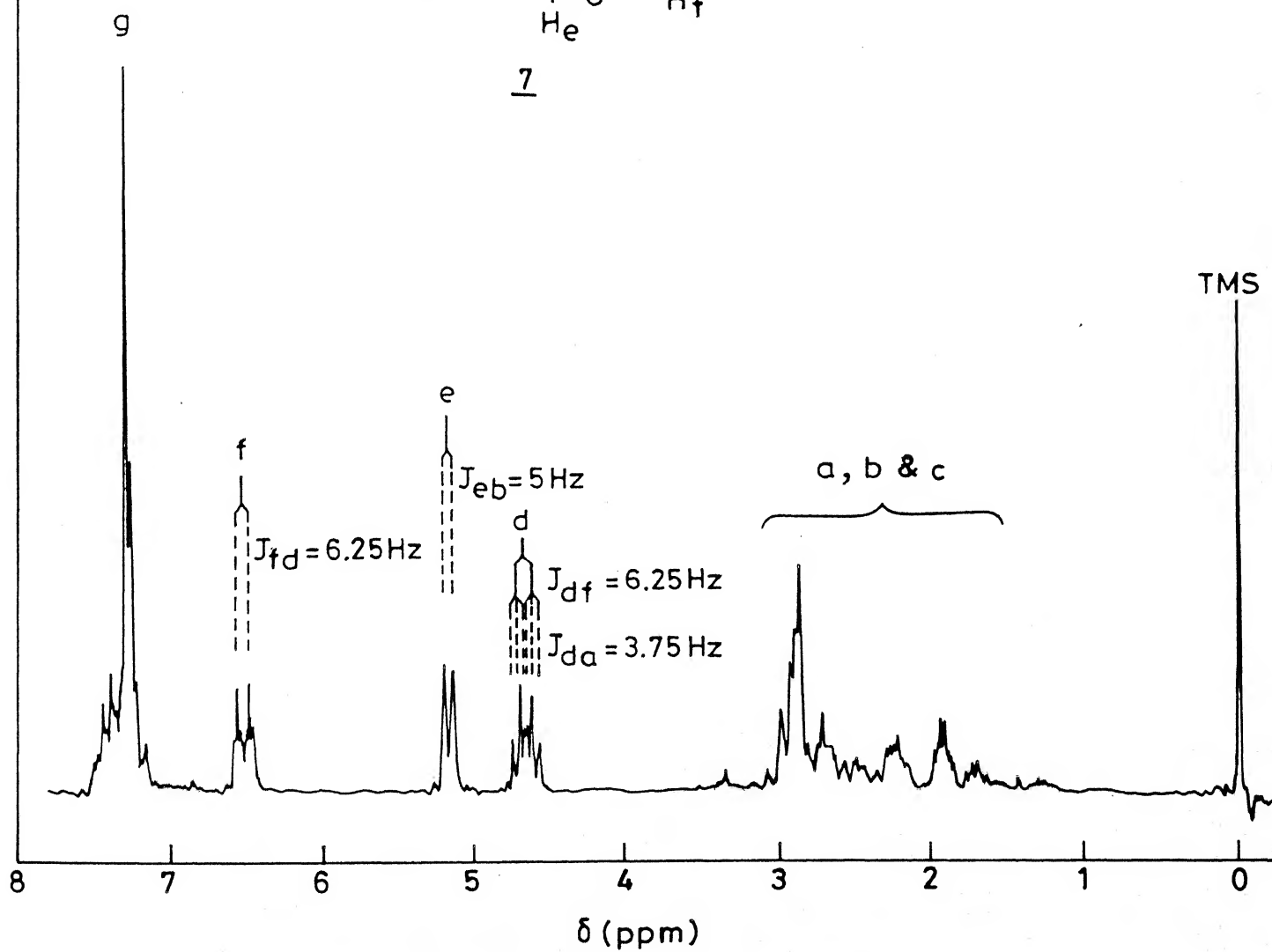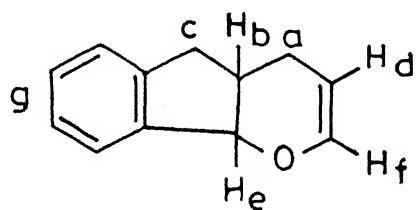
^{1}H NMR spectrum (80 MHz) of $\underline{7}$.
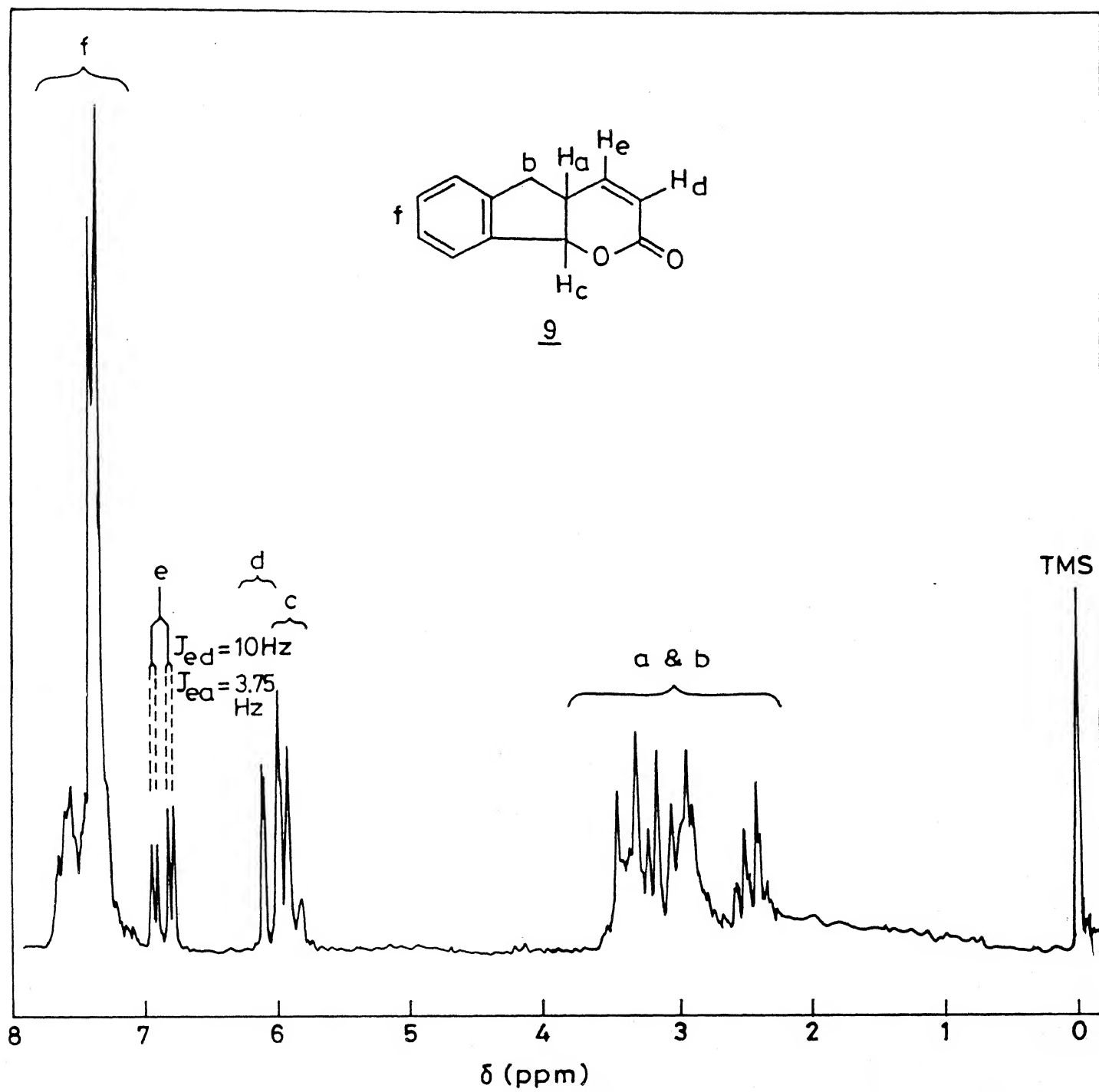
^{1}H NMR spectrum (80 MHz) of $\underline{9}$.
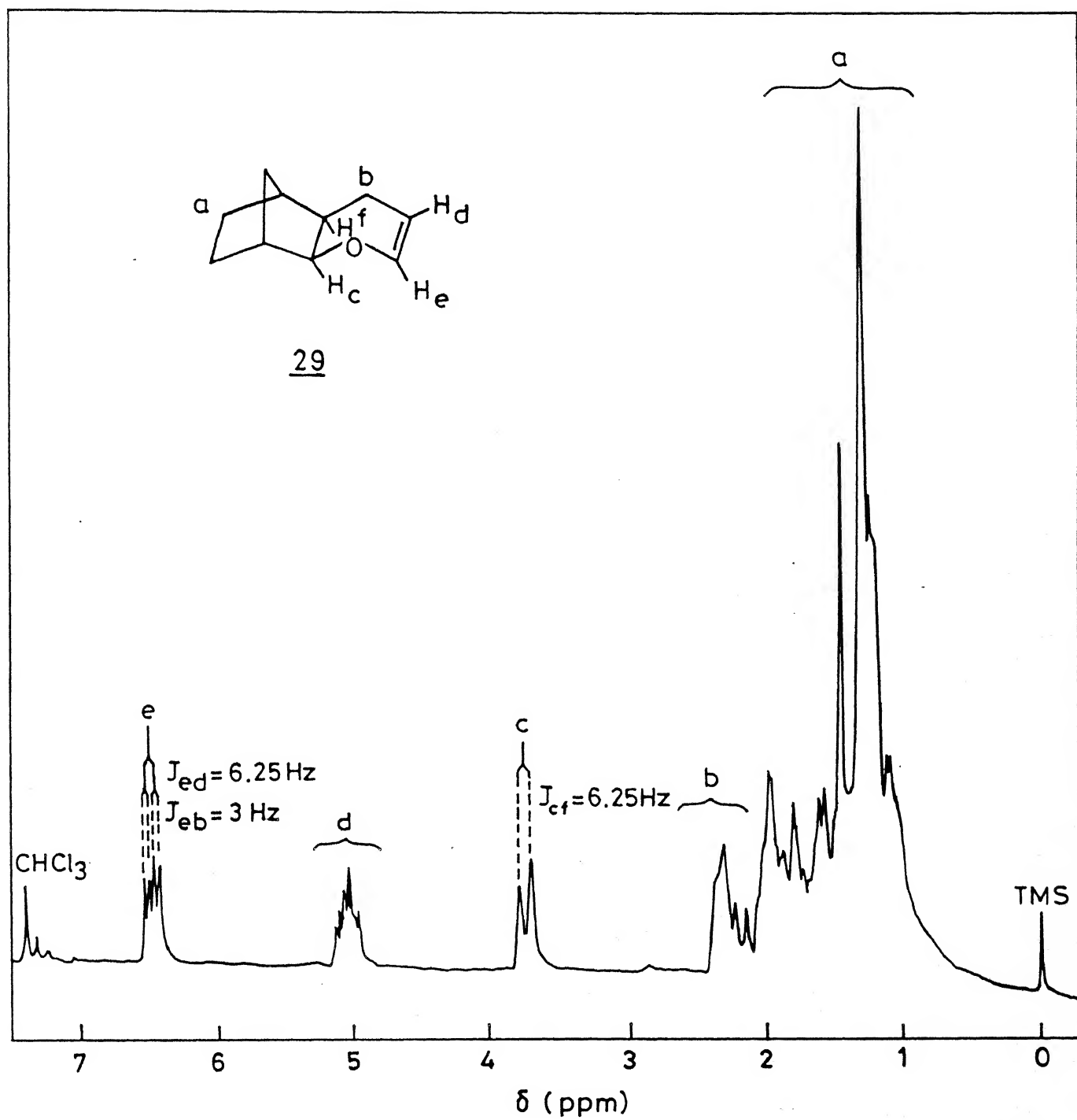
^{1}H NMR spectrum (80 MHz) of 29.
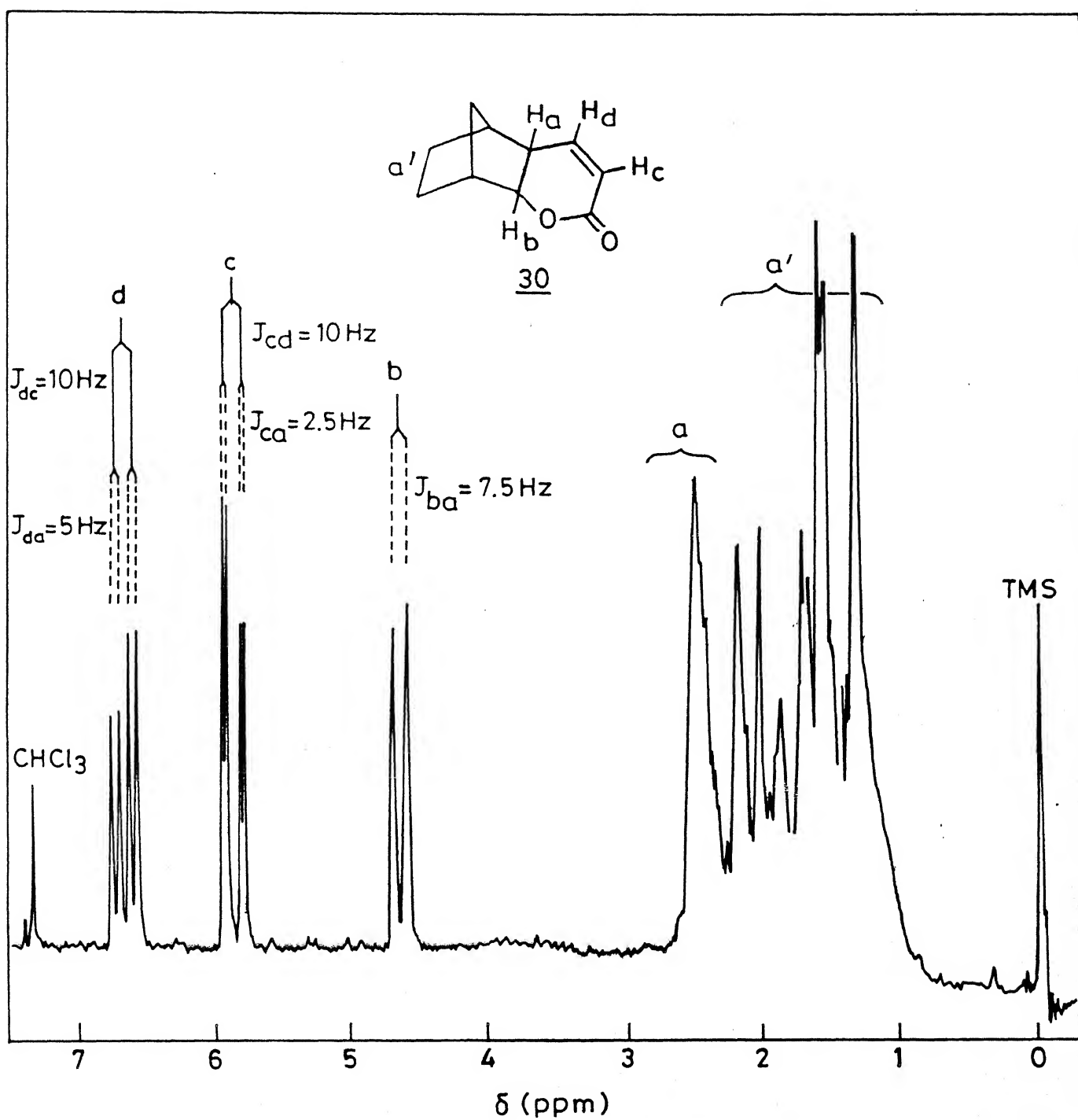
^{1}H NMR spectrum (80 MHz) of 30.

^{1}H NMR spectrum (80 MHz) of <u>30a</u>.

In order to find out whether the present methodology can be used to synthesize α,β-unsaturated esters from acylic enol ethers 1-ethoxy heptene 17[24] and 1-ethoxy octene 19[25] were prepared from the corresponding diethylacetal 16 and 18 respectively[24,25a,c,d] (Scheme I. B. 9).

1-Ethoxy heptene 17 on treatment with PDC/t-BuOOH in benzene gave ethyl heptanoate 20 (Scheme I. B. 9) in 39% yield along with a non-polar compound, presumably t-butyl peroxy compound, which decomposed under the conditions of purification. This unidentified peroxy compound appears to be the major compound as revealed by TLC. Similarly 1-ethoxy octene 19 under identical reaction conditions gave ethyl octanoate 21 (Scheme I. B. 9) in 20% yield along with the unidentified t-butyl peroxy compound. ^{1}H NMR of the crude products in both the above reactions indicate the presence of t-butyl peroxy compound.

Having shown that the pyridinium dichromate/t-butyl hydroperoxide reagent system effects the transformation of cyclic enol ethers to α,β-unsaturated lactones, it was decided to apply this novel oxidative rearrangement methodology to the synthesis of (±)-argentilactone 25, (±)-goniothalamin 27 and (±)-goniothalamin oxide 28.

Synthesis of (±) argentilactone 25

(±) Argentilactone 25 was synthesized by using our oxidative rearrangement methodology and is presented in Scheme I. B. 10. Accordingly dihydropyran-2-carboxaldehyde 22 was prepared by the

SCHEME I.B.8
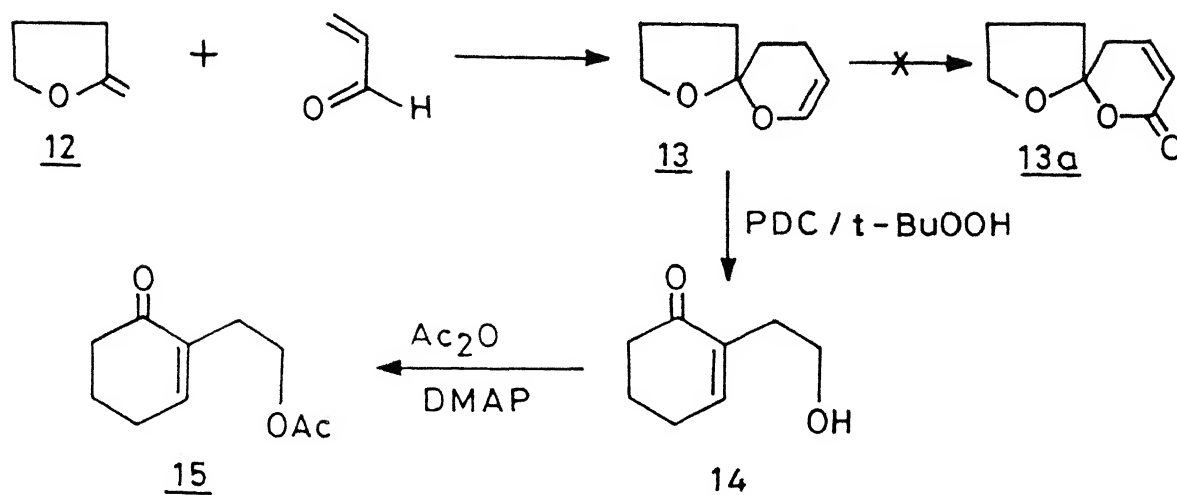
SCHEME I.B.9
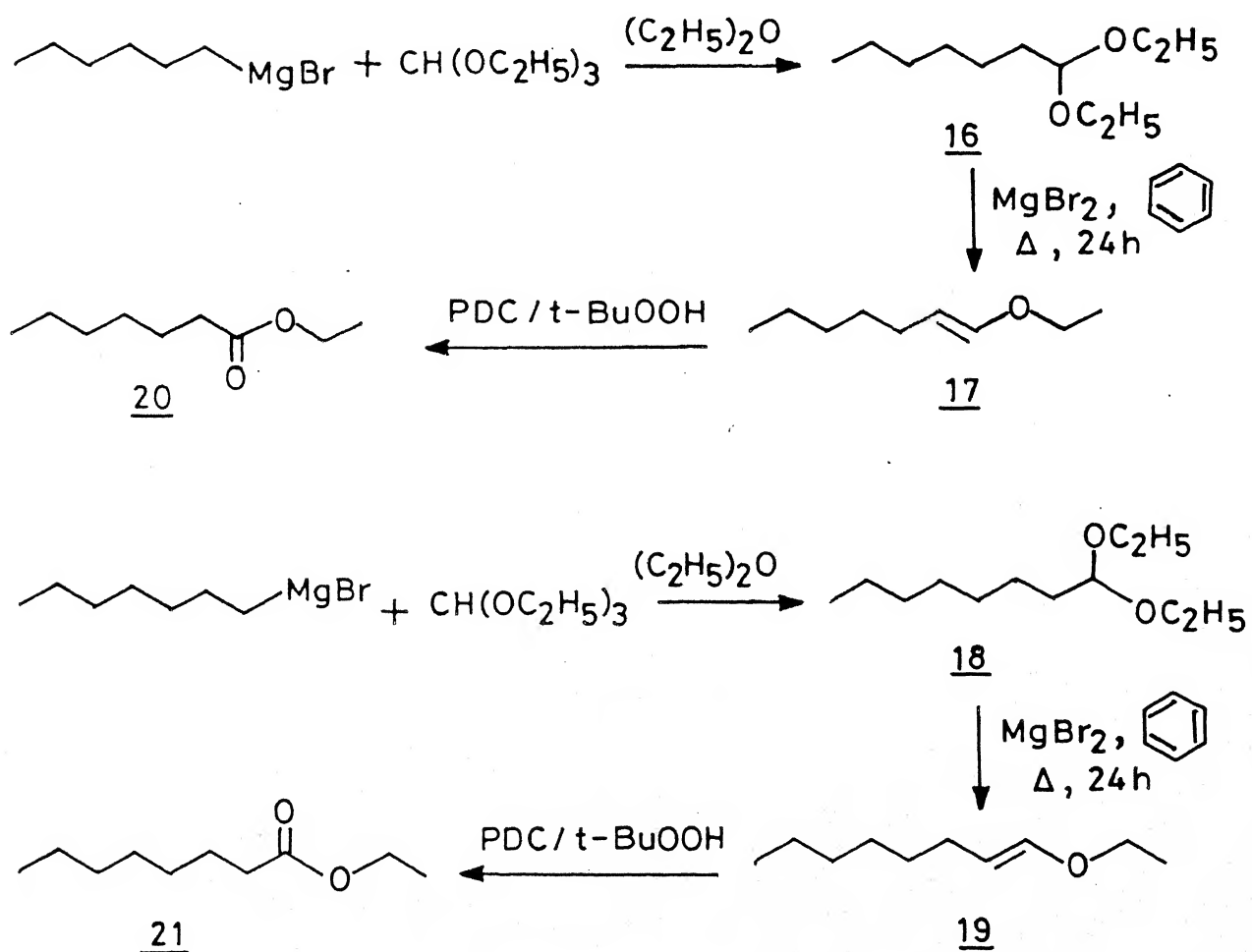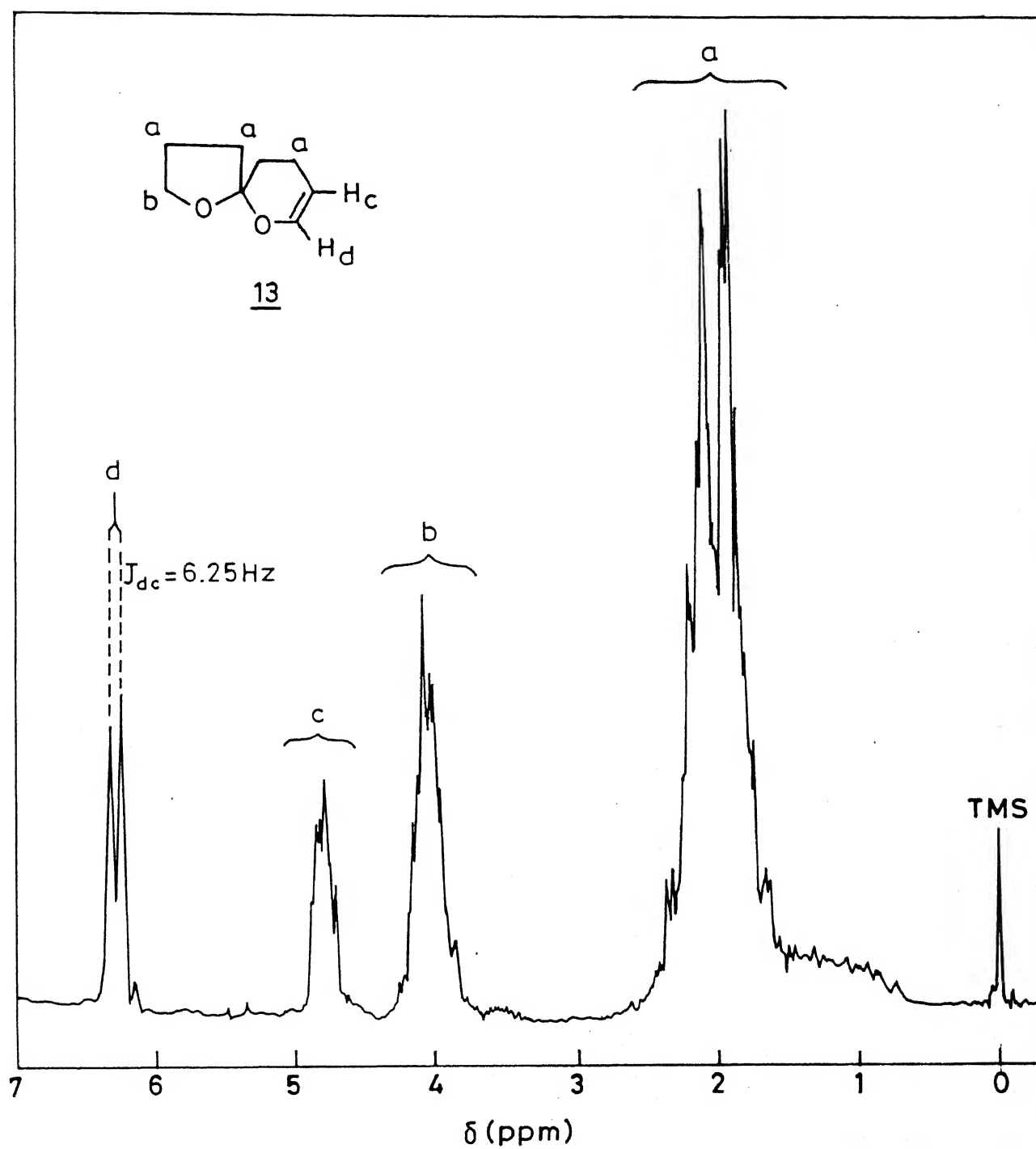
^{1}H NMR spectrum (80 MHz) of 13 .
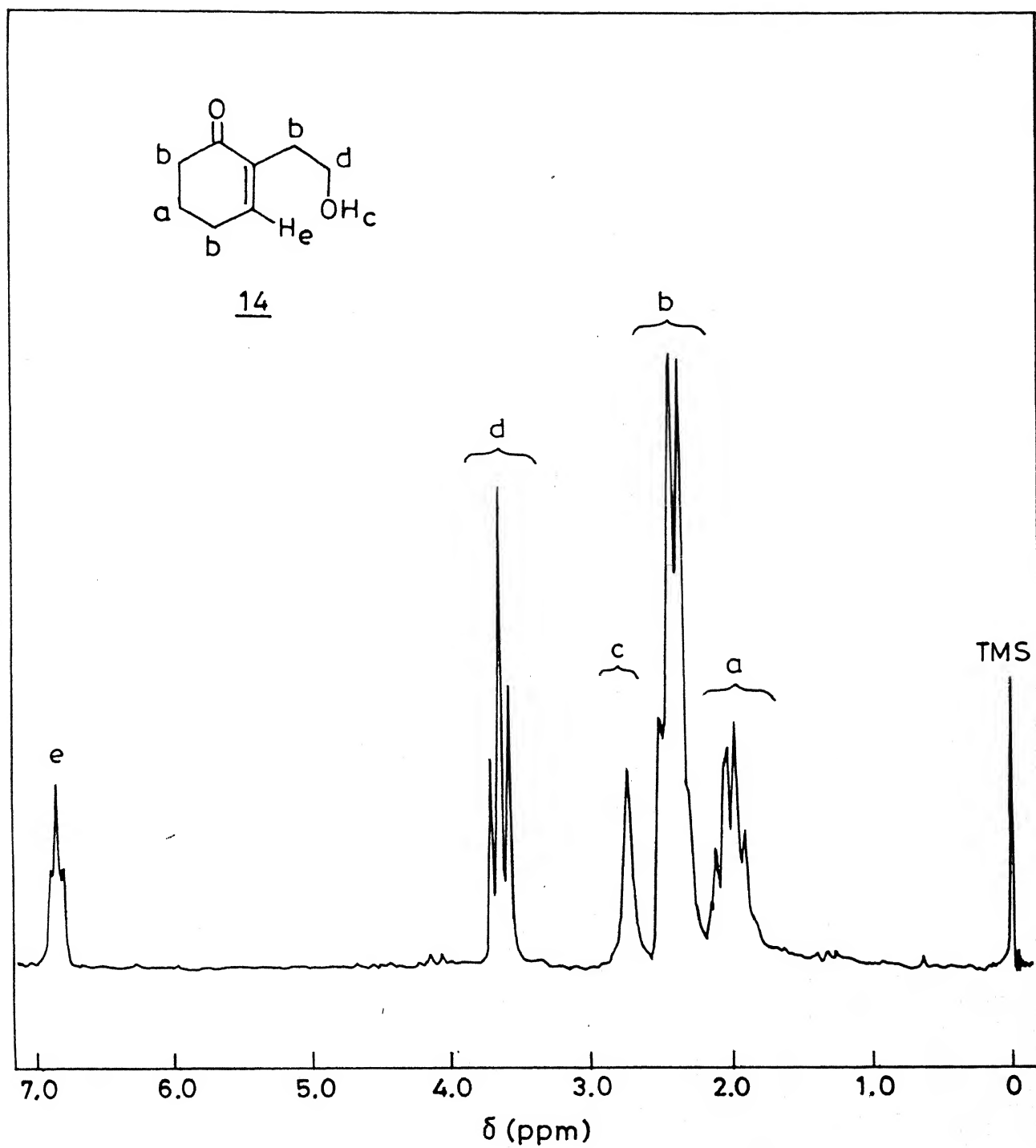
^{1}H NMR spectrum (90 MHz) of 14.

thermal dimerization of acrolein.[26] Wittig reaction of __22__ with hexyltriphenylphosphonium bromide afforded 2-(Z)-1-heptenyl-3,4-dihydro-2H-pyran __23__ in 71% yield.[12] Oxidation of __23__ with PDC / t-BuOOH (1:2:3) at 0°C for 4 h yielded (+) argentilactone __25__ in 40% yield along with the t-butyl peroxy compound __24__ (25%). Compound __24__ on exposure to triethylamine in toluene at 60°C for 1 h got converted smoothly to the , -unsaturated lactone __25__. Thus the combined yield of argentilactone __25__ in this reaction worked out to be quite reasonable (52%).

Synthesis of (+)goniothalamin __27__ and (+)goniothalamin oxide __28__

The synthetic route employed for the synthesis of __27__ and __28__ is outlined in Scheme I. B. 11. Wittig reaction of dihydropyran-2-carboxaldehyde __22__[26] with benzyldiethyl phosphite[27,28] in the presence of butyllithium and HMPA afforded (E)-6-(2-phenylvinyl)-3,4-dihydro-2H-pyran __26__ in 39% yield. Enol ether __26__ when treated with PDC/t-BuOOH at 0°C for 3 h gave after purification (+)goniothalamin __27__ (26%) and the t-butyl peroxy compound __27a__ (14%). Further reaction of __27a__ with triethylamine in toluene at 80°C for 0.5 h resulted in the formation of __27__. Thus the total yield of (+)goniothalamin in this reaction was 35%. (+) Goniothalamin __27__ on treatment with m-chloroperbenzoic acid afforded (+) goniothalamin oxide __28__[18] (74%)

SCHEME I.B.10
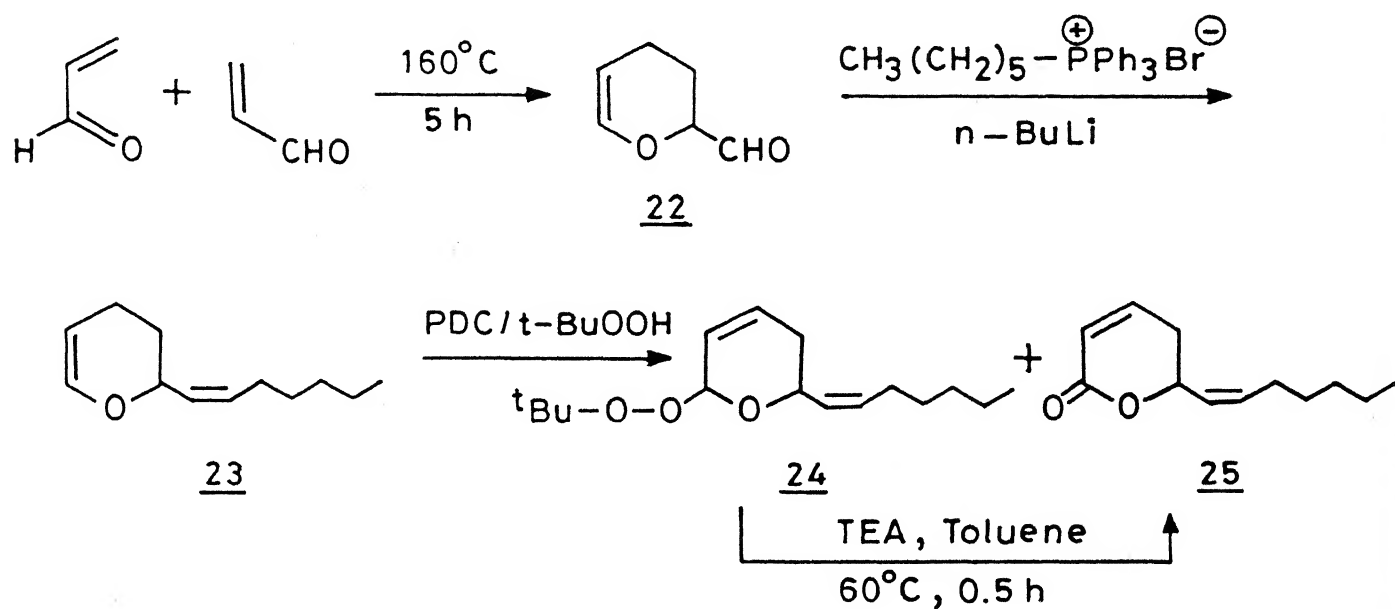
SCHEME I.B.11
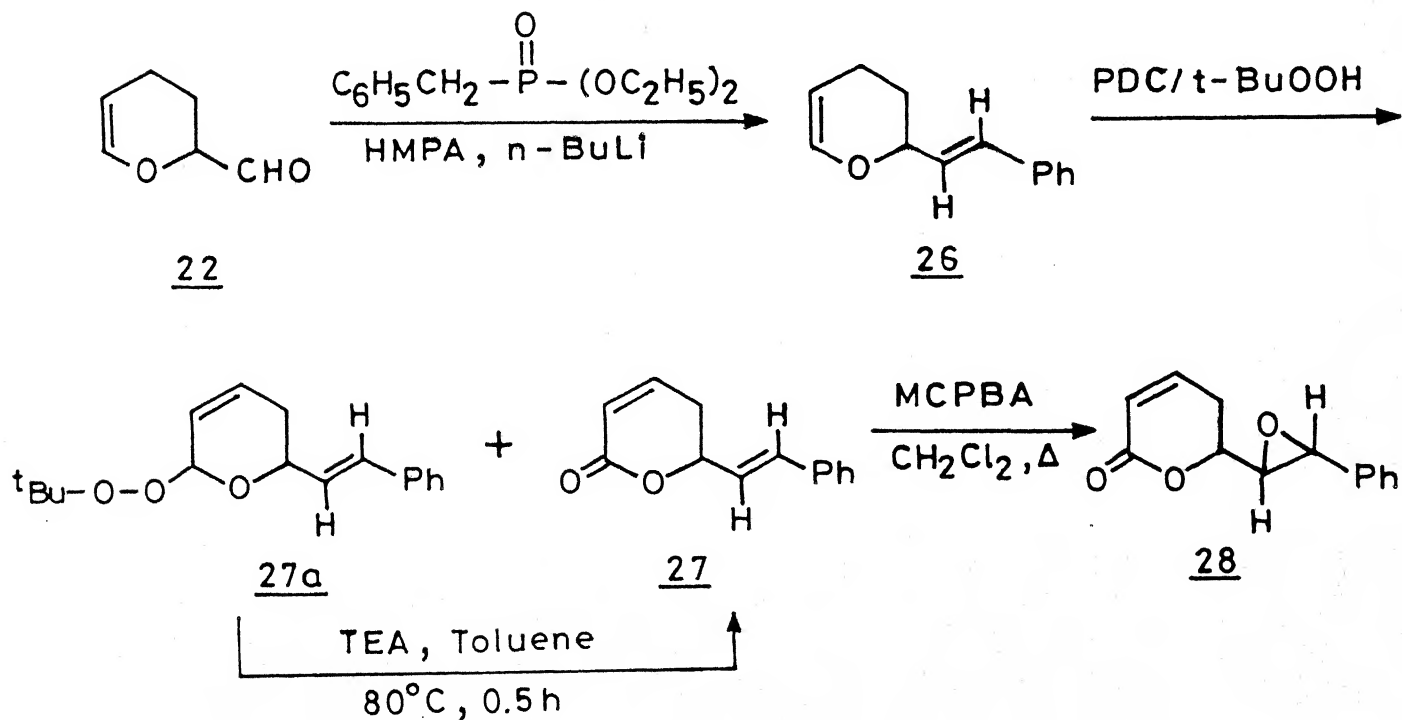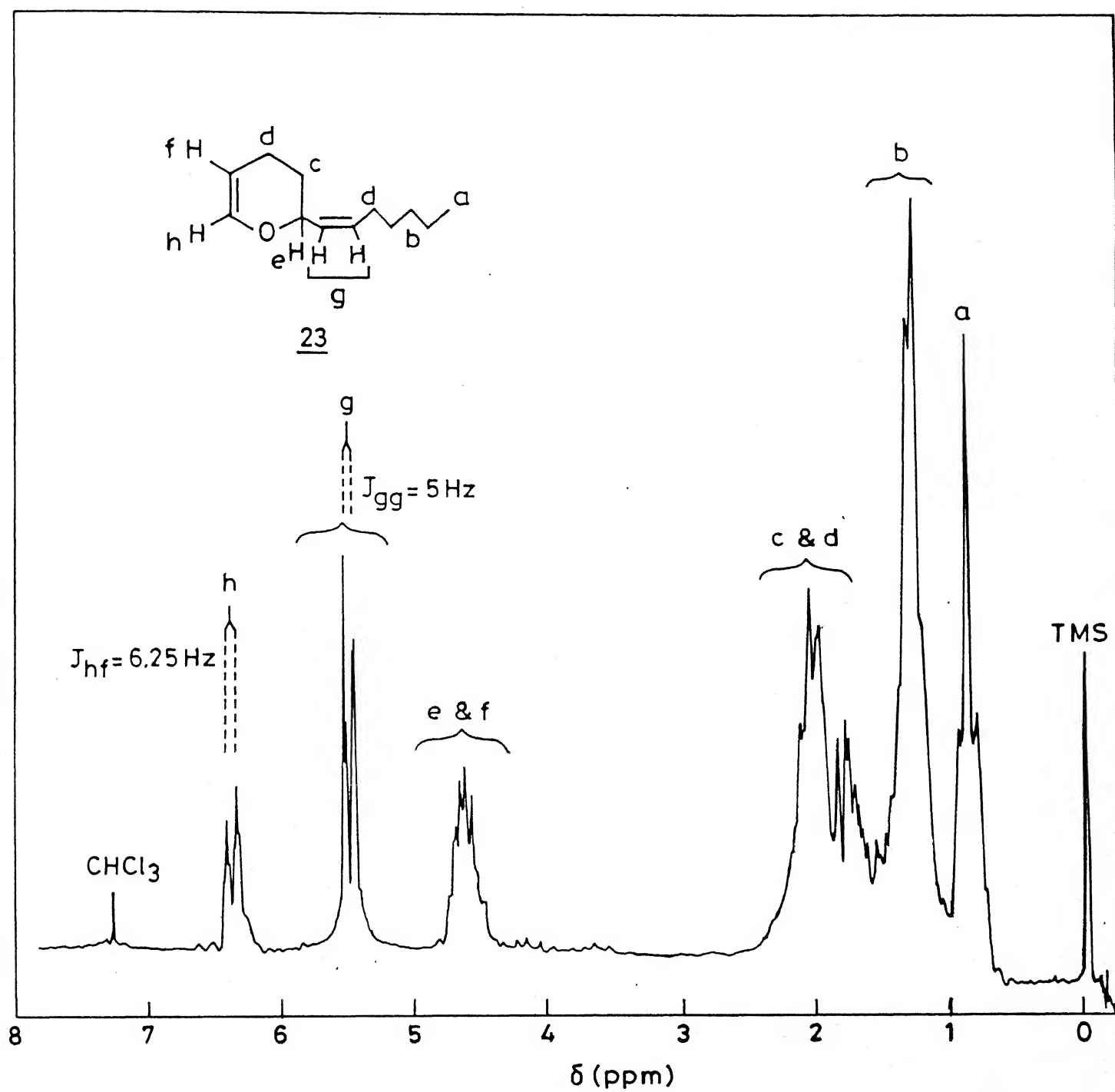
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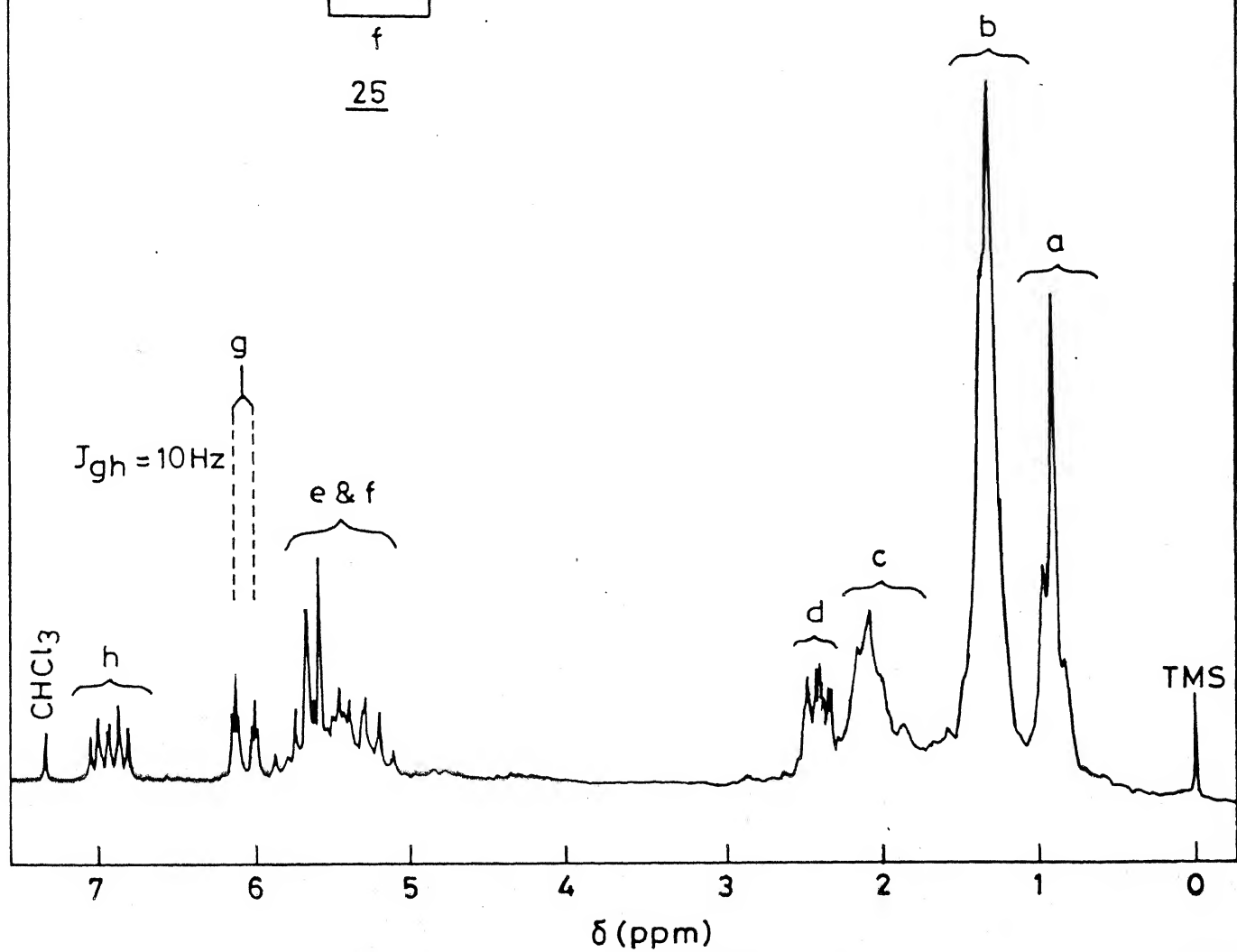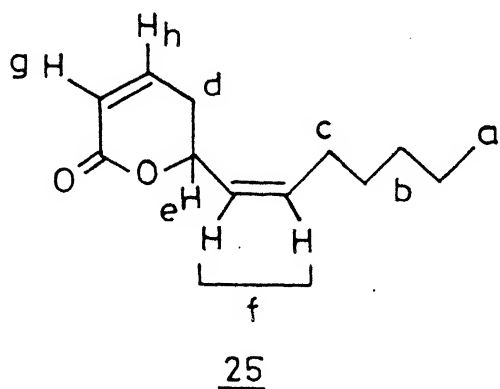
^{1}H NMR spectrum (80 MHz) of **25**.
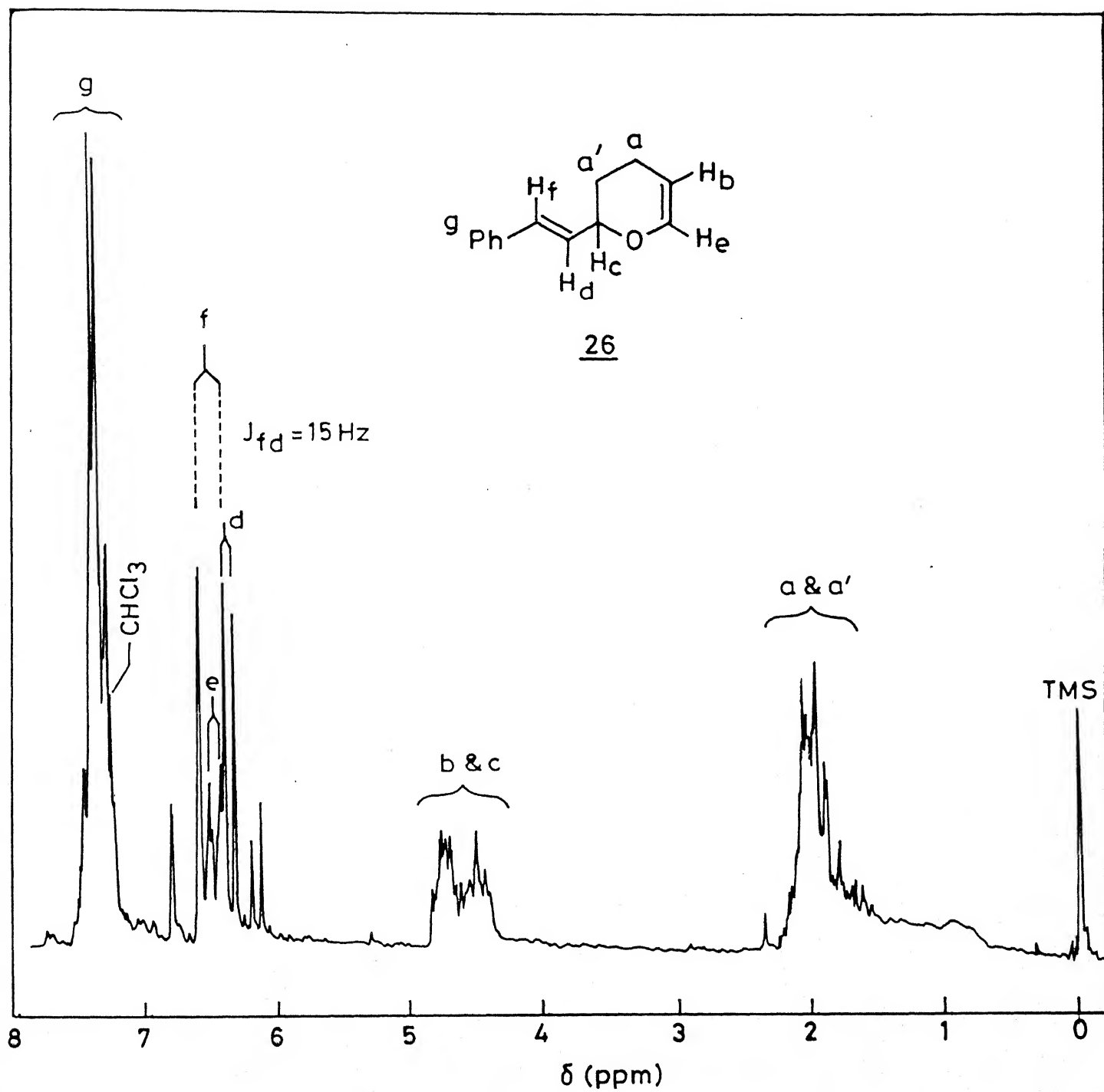
^{1}H NMR spectrum (80 MHz) of 26.
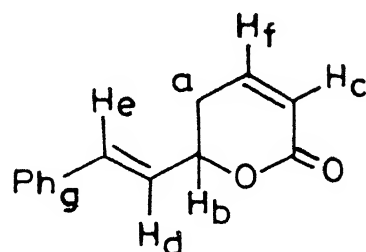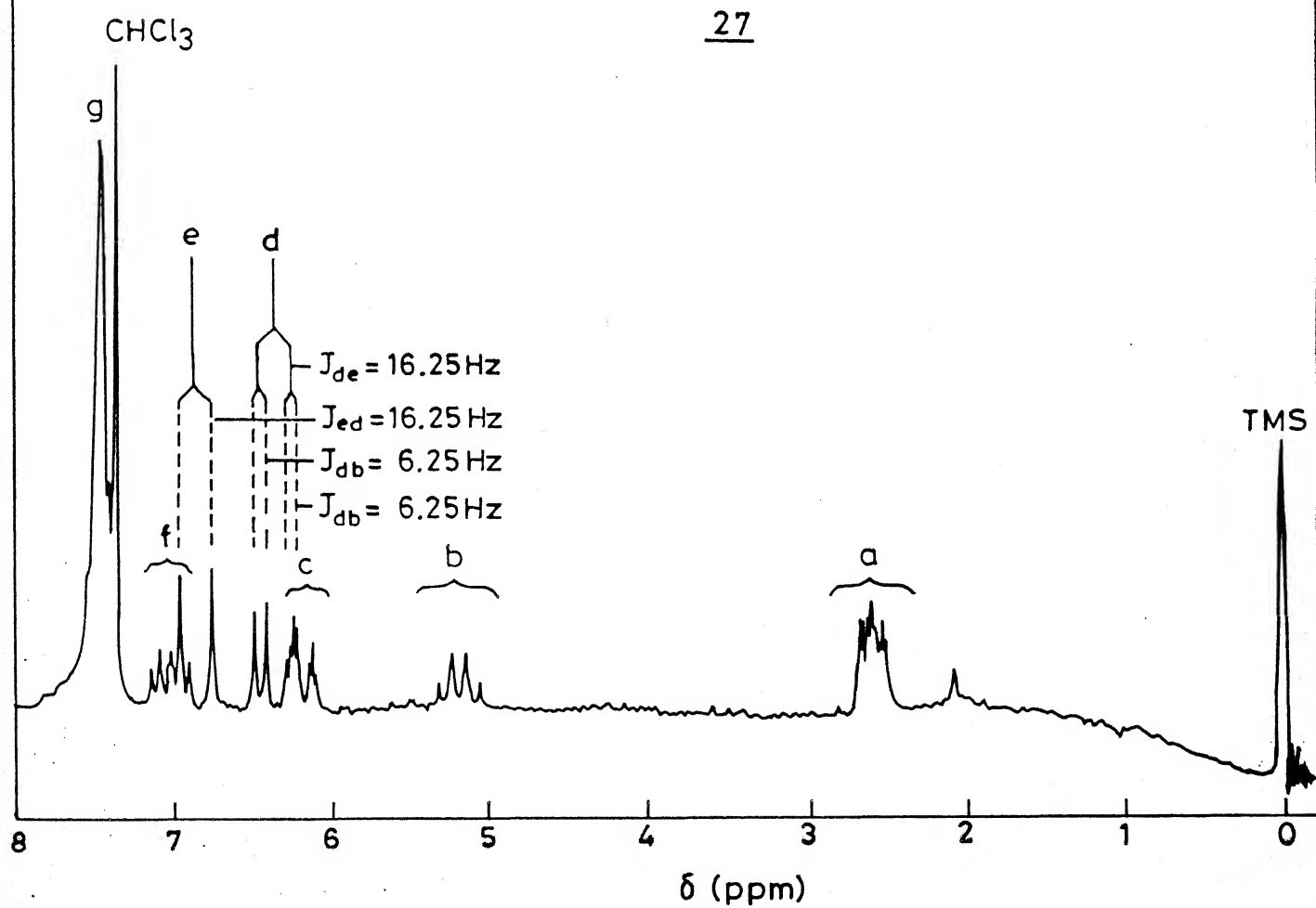
^{1}H NMR spectrum (80 MHz) of 27.
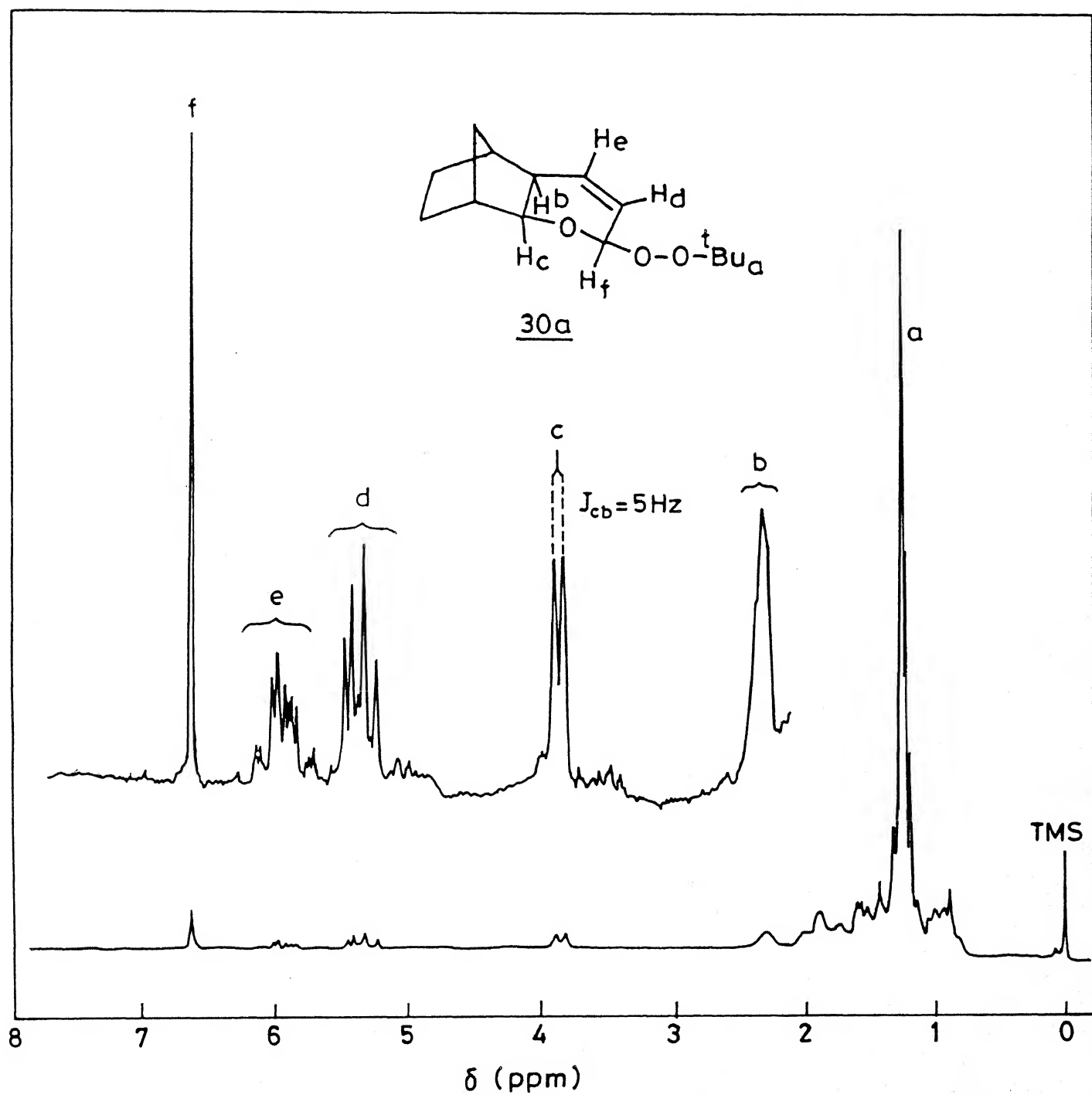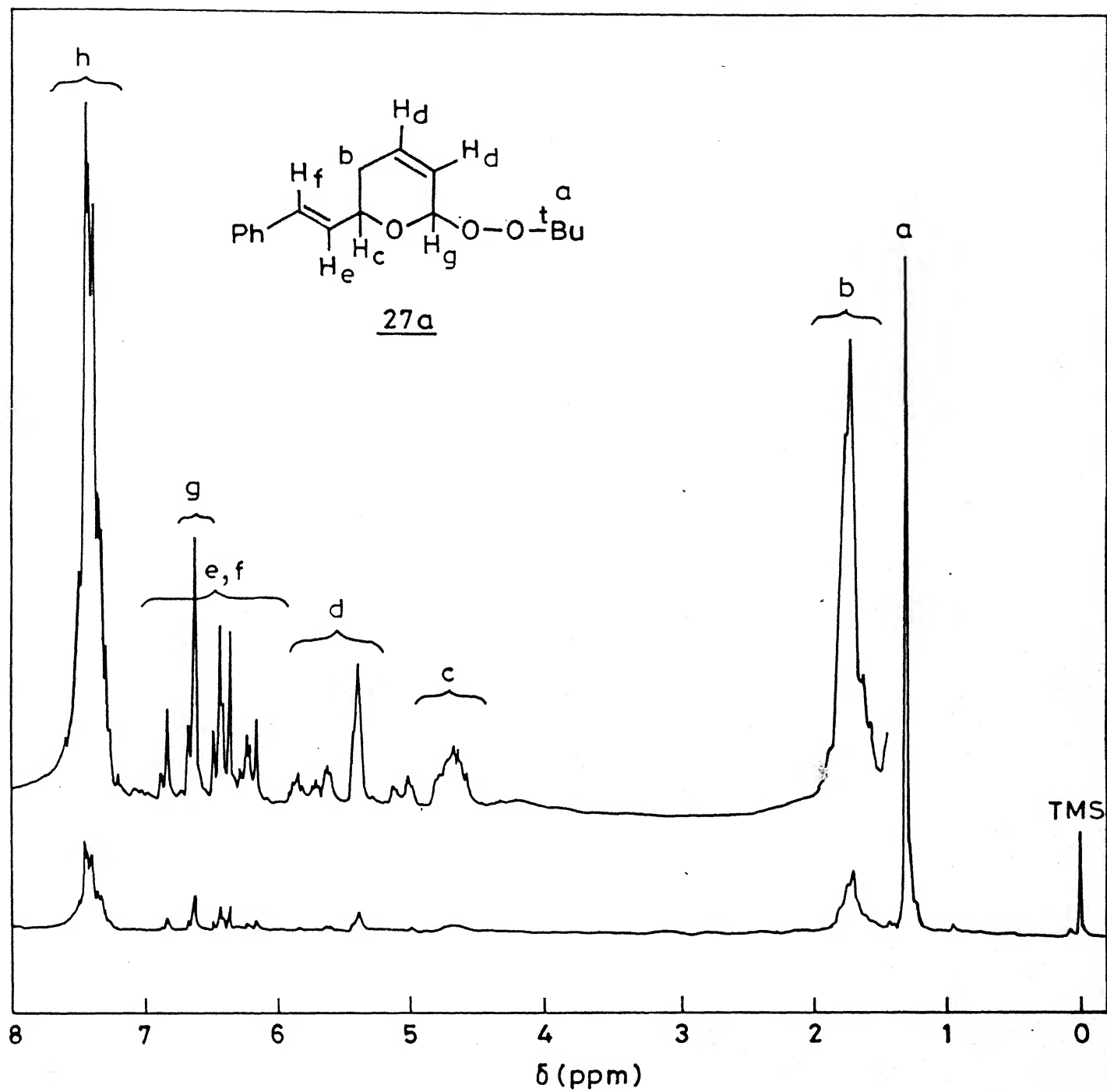
^{1}H NMR spectrum (80 MHz) of __27a__.

I.2.c Experimental

General Procedures

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, tlc, m.p.).

Materials

Commercial grade solvents were distilled prior to use. Benzene was distilled after storing over calcium chloride and kept over sodium wire. Petroleum ether fractions 60-80°C were used for chromatography. Dichloromethane was distilled over phosphorous pentoxide and stored over molecular sieves (4 $\overset{o}{A}$). Pyridine was distilled over potassium hydroxide pellets. Chromium trioxide flakes (BDH, E. Merck) and 70% t-butyl hydroperoxide (Koch Light Laboratories Ltd.) were used as such. Acetic anhydride was distilled from phosphorous pentoxide prior to use. Dimethyl amino pyridine (DMAP) was obtained from Aldrich Chemicals Co. (m.p. 108-110°C) and used as such.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) Ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of

phosphomolybdic acid in ethanol followed by heating to <u>ca</u>. 200°C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and then reimmersion and heating to <u>ca</u>. 200°C.

Column chromatography was performed using 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel. Enol ethers were purified using basic alumina (Riedel).

Physical data

Melting points (m.p.) were determined with a Uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Bulb to bulb distillation was carried out on a Büchi-GKR-50 distillation unit.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80 instrument. [13] Carbon (CMR) spectra were recorded at 22.5 MHz on a Jeol FX 90q instrument. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane

(TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), etc. Coupling constants are reported wherever necessary and are expressed in Hz. Mass spectra (MS) were recorded on a Jeol JMS-D 300 mass spectrometer. Principal molecular fragments are reported.

Oxidation of dihydropyran 1 to dihydro-2-pyrone 3 with PDC/t-BuOOH

Pyridinium dichromate (4.123 g, 10.96 mmol) was taken in a 25 mL round bottomed flask in dichloromethane (12 mL) and the flask was cooled in an ice bath. t-Butyl hydroperoxide (1.482 g, 16.44 mmol, 1.58 mL) was added to pyridinium dichromate and was stirred for 15 min. The reagent generated in solution was quickly filtered over a cotton plug into another 25 mL round bottomed flask kept in an ice bath, the residue was washed with dichloromethane (3 mL) and filtered. To this dihydropyran 1 (0.461 g, 5.48 mmol, 0.5 mL) in dichloromethane (5 mL) was added dropwise and the reaction was stirred for 2 h at $0^{\circ}C$. The completion of reaction could be observed by the formation of green Cr^{3+} deposits on the walls of the flask. Dichloromethane was evaporated under vacuum, ether (15 mL) was added and filtered over a small pad of Celite. After evaporating the ether, the crude product obtained was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether, 5 : 95) to give the peroxy compound 2 (0.055 g, 5.9%).

IR (CHCl$_3$)   : 3000, 2950, 1660, 1365, 1090, 1000, 955 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.26 (s, 9H), 2.17 (m, 2H), 3.67-4.1 (m,2H)

4.27 (br s, 1H) 4.6-4.87 (m, 1H)

6.5 (d, 1H, J = 6Hz).

Further elution (ethyl acetate : petroleum ether, 20 : 80) afforded the dihydro-2-pyrone 3[3],[7] (0.269 g, 50%).

IR (CHCl$_3$)   : 3010, 1720, 1590 cm^{-1}

^{1}H NMR (CDCl$_3$) : 2.36-2.56 (m, 2H, CH$_2$), 4.42-4.50 (t, 2H,

CH$_2$O, J=6.25 Hz), 5.97 and 6.08 (dt, CH=CH-CO,

J = 2.5 and 10 Hz), 6.85-6.95 (dt, CH=CHCO,

J = 10 Hz).

Conversion of 2 to 3

To a stirred solution of 2 (0.05 g, 0.291 mmol) in toluene (4 mL) was added triethylamine (0.029 g, 0.116 mmol, 0.04 mL) and heated at 80°C for 0.5 h. The reaction mixture was cooled, water (1 mL) was added and extracted with ether. The ether extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product obtained was purified by flash chromatography to yield the α,β-unsaturated lactone 3 (0.025 g), which was compared by TLC, IR and ^{1}H NMR and found to be identical to the lactone obtained above.

Preparation of 5,6-indenyldihydro-2H-pyran[20] 7

Indene 6 (5 g, 43 mmol, 5.02 mL) and acrolein (7.24 g, 129.13 mmol, 8.6 mL) were sealed in a glass tube under N$_2$. This was heated in an oil bath at 140°C for 10 h. The seal was carefully

broken after the contents were cooled in an ice bath. The crude reaction product was purified over basic alumina to recover unreacted starting material $\underline{6}$ (2.3 g) and the adduct $\underline{7}$ (1.6 g, 40%) as a pale yellow oil.

IR (neat)   : 3030, 2910, 2840, 1650, 1235, 1085, 1060, 1050 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.81-2.33 (m, 3H), 2.86 (m, 2H, $C_6H_5-C\underline{H}_2$),

4.53-4.76 (dt, 1H, $-O-CH=C\underline{H}-$ J=3.75 and 6.25Hz),

5.17 (d, 1H, $C_6H_5-C\underline{H}-O-$, J=5 Hz), 6.52

(dt, 1H, $-O-C\underline{H}=CH$, J=2.5 and 6.25 Hz),

7.29 (d, 4H, aromatic).

Oxidation of 5,6-indenyldihydro-2H-pyran $\underline{7}$ with PDC/t-BuOOH

5,6-Indenyldihydro-2H-pyran $\underline{7}$ (0.213 g, 1.24 mmol) in dichloromethane (3 mL) was added to the oxidant at $0°C$ generated as above from pyridinium dichromate (0.932 g, 2.48 mmol) and t-butyl hydroperoxide (0.335 g, 3.72 mmol, 0.36 mL). The reaction was allowed to come to room temperature over a period of 4 h. Work up of the reaction mixture as described earlier gave a residue which on chromatographic purification over silica gel (ethyl acetate : petroleum ether, 1 : 9) yielded the peroxy compound $\underline{8}$ (0.122 g, 38%).

IR (CHCl$_3$)   : 3020, 3000, 2950, 1620, 1200-1000 cm^{-1}

^{1}H NMR (CDCl$_3$) : 1.35 (s, 9H, -C<-), 2.94 (m, 2H), 5.31 (d, 2H),

5.56 (dd, 1H), 5.76 - 6.0 (dd, 1H), 6.29 - 6.51

(dd, 1H), 7.35 (m, 4H, aromatic).

MS (m/e)   : 171($M^+-C_4H_9O_2$), 129, 128, 116, 115.

Further elution with (ethyl acetate : petroleum ether, 20 : 80) yielded the α,β-unsaturated lactone 9 (0.100 g, 43%) as an oil.

IR (CHCl₃) : 3070, 3025, 2930, 1725, 1605, 820, 750 cm^{-1}.

^{1}H NMR (CDCl₃) : 2.87 - 3.50 (m, 3H), 5.93 (d, 1H, J = 6.25 Hz)

5.97 and 6.07 (dd, 1H, J = 1.25 and 10 Hz),

6.78 and 6.91 (dd, 1H, J=3.75 and 10 Hz), 7.31

(4H, aromatic).

MS (m/e) : 186(M$^+$), 141, 129, 128, 116, 115.

Conversion of 8 to 9

A stirred solution of 8 (0.1 g, 0.385 mmol) in toluene (4 mL) and triethylamine (0.039 g, 0.077 mmol, 0.054 mL) was heated at 80°C for 0.5 h. The reaction mixture was cooled, water (1 mL) was added and extracted with ether. The ether extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product obtained was purified by flash chromatography to yield the α,β-unsaturated lactone 9 (0.061 g), which was compared by TLC, IR and ^{1}H NMR and found to be identical to the lactone obtained above.

Preparation of 5,6-norbornyl-3,4-dihydro-2H-pyran 29 [29]

A solution of freshly distilled acrolein (4.485 g, 0.08 mol, 5.35 mL) norbornylene (10 g, 0.106 mol) and BHT (2,6-di-t-butyl p-cresol; 0.16 g) were introduced into a glass tube and sealed after cooling the contents in an ethanol-liquid nitrogen bath and heated at 190°C for 25 h. The seal was carefully broken after cooling the contents in an ethanol-liquid nitrogen bath.

The crude product on chromatographic purification over basic alumina (2% ether in petroleum ether 40-60°C) gave the pure enol ether 29 (6.515 g, 54%).

IR (neat)   : 3050, 2940, 2870, 1640 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.09-2.41 (br s, 2H), 3.75 (d, 1H, J=6.25 Hz)

                      4.92-5.16 (m, 1H), 6.47 (dd, 1H, J=3 and 6.25 Hz).

Oxidation of 5,6-norbornyl-3,4-dihydro-2H-pyran 29 with
PDC/t-BuOOH

     Enol ether 29 (0.4 g, 2.67 mmol) in dichloromethane (2 mL) was added to the oxidant at 0°C generated as above from pyridinium dichromate (2.0 g, 5.34 mmol) and t-butyl hydroperoxide (0.722 g, 8.01 mmol, 0.77 mL). The reaction was allowed to come to room temperature over a period of 3 h, work up of the reaction mixture as described earlier gave a residue which on chromatographic purification over silica gel initially using (ethyl acetate:petroleum ether, 5:95) yielded the t-butyl peroxy compound 30a (0.115 g, 18%).

IR (neat)   : 2950, 2875, 1360, 1195, 1100 cm^{-1}

^{1}H NMR (CDCl$_3$) : 1.27 (s, 9H), 2.33 (br s, 1H), 3.87 (d, 1H

                   J = 5Hz), 5.17-5.55 (m, 1H), 5.95 (dd, 1H),

                   6.61 (s, 1H).

MS (m/e)   : 151 (M+2), 149, 91, 81, 57.

Further elution with (ethyl acetate:pertoleum ether, 1:9) gave the pure α,β-unsaturated lactone 30 (0.185 g, 42%).

IR (neat)   : 3010, 2950, 2875, 1725, 1650 cm^{-1}

^{1}H NMR (CDCl$_3$) : 2.52 (br s, 2H), 4.64 (d, 1H, J = 7.5 Hz), 5.87

(dd, 1H, J=2.5 & 10 Hz), 6.69 (dd, 1H, J=5&10 Hz).

Conversion of 30a to 30

To a stirred solution of 30a (0.08 g, 0.336 mmol) in toluene (4 mL) was added triethylamine (0.034 g, 0.336 mmol, 0.047 mL) and heated at 80°C for 0.5 h. The reaction mixture was cooled, water (1 mL) was added and extracted with ether. The ether extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product obtained was purified by flash chromatography to yield the α,β-unsaturated lactone 30 (0.043 g), which was compared by TLC IR and ^{1}H NMR and found to be identical to the lactone obtained above.

Preparation of tetrahydro furfuryl chloride 11[23]

In a 250 mL two necked round bottomed flask fitted with a mechanical stirrer and a dropping funnel were placed freshly distilled tetrahydro furfuryl alcohol 10 (15.81 g, 0.155 mole, 15 mL) and pyridine (13.47 g, 0.17 mole, 13.8 mL). Freshly distilled thionyl chloride (19.34 g, 0.16 mole, 11.9 mL) was added dropwise to the rapidly stirred and cooled mixture in an ice bath. After the addition of a portion of thionyl chloride, a pasty crystalline mass separated and the temperature began to rise. Addition of thionyl chloride was controlled such that the temperature was not allowed to raise above 60°C. The solid mass

redissolved on addition of the remaining thionyl chloride, ice bath was removed and stirred for 3-4 h. The liquid was extracted with ether and the combined ethereal layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product thus obtained was distilled under vacuum to yield tetrahydro furfuryl chloride 11 (13.16 g, 70.5%).

b.p.   : 53 - 54°C/20 mm (lit.[23] b.p. 41 - 42°C/11 mm).

Preparation of tetrahydro-2-methylene furan 12[21a,b,22]

To a suspension of powdered potassium hydroxide (5.22 g, 93.2 mmol) in a 25 mL round bottomed flask was added 2-(chloro-methyl) tetrahydro furan 11 (4.995 g, 41.4 mmol, 4.5 mL). A fractional distillation assembly was attached with a receiver flask containing few potassium hydroxide pellets and the contents were refluxed for 8 h by maintaining the oil bath temperature at 120°C. The temperature was gradually increased from 120°C to 180°C, tetrahydro-2-methylene furan 12 starts distilling and was collected at 0°C and was redistilled using a fractionating column to yield 12 (2.787 g, 80%).

b.p.   : 98 - 99°C (lit.[21b] b.p. 98 - 99°C).

IR (neat)   : 3090, 2960, 2860, 1665, 1175, 1040 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 1.8-2.2 (m, 2H), 2.5 (m, 2H), 3.8 (m, 1H)

4.0,4.1 (2d, 2H, J = 6.5 Hz), 4.1 (m, 1H).

Preparation of 1,6-dioxaspiro[4.5]dec-7-ene 13[21b]

Tetrahydro-2-methylenefuran 12 (2.787 g, 33.18 mmol) and hydroquinone (0.036 g, 0.33 mmol) were taken in a 25 mL round bottomed flask. To this freshly distilled acrolein (1.860 g, 33.18 mmol, 2.2 mL) was added and allowed to stand at room temperature for 6 days and distilled by Kugelrohr distillation assembly to give 1,6-dioxaspiro[4.5]dec-7-en 13 (3.155 g, 68%).

b.p.　　　　　: 80-82°C/25 mm (lit.[21b] b.p. 80-82°C/25 mm)

IR (thin film)　: 3050, 1645, 1245, 1060, 1020 cm^{-1}.

^{1}H NMR (CDCl$_3$)　: 1.6-2.3 (m, 8H, CH$_2$), 4.0 (m, 2H, CH$_2$O),

4.75 (m, 1H, CH=CH-O-),

6.17 (d, 1H, CH=CH-O-, J = 6.25 Hz)

Oxidation of 1,6-dioxaspiro[4.5]dec-7-ene 13 with pyridinium dichromate/t-butyl hydroperoxide

To the oxidant generated as described earlier in dichloromethane (10 mL) at 0°C from pyridinium dichromate (2.499 g, 6.64 mmol) and t-butyl hydroperoxide (0.897 g, 9.96 mmol, 0.96 mL) was added dropwise 1,6-dioxaspiro[4.5]dec-7-en (0.465 g, 3.32 mmol) in dichloromethane (5 mL). Similar workup and purification gave an intensely UV active oily compound which was found to be 2-(2-hydroxy ethyl)cyclohex-2-enone 14 (0.235 g, 50.5%).

IR (CHCl$_3$)　　: 3460, 3020, 1665 cm^{-1}.

^{1}H NMR (CDCl$_3$)　: 2.0 (m, 2H), 2.3-2.6 (m, 6H), 2.75 (s, 1H),

3.55-3.8 (t, 2H, -CH$_2$OH), 6.85 (t, 1H, -CH=C-C-).

^{13}C NMR (CDCl$_3$) :   200.5(s), 148.1(d), 137(s), 61.6(t), 38.4(t),

33.4(t), 26.1(t), 23(t).

MS (m/e)   : 140(M$^+$).

Acetylation of 2-(2-hydroxy ethyl)cyclohex-2-enone 14

To a mixture of 2-(2-hydroxyethyl)cyclohex-2-enone 14 (0.127 g, 0.907 mmol), dimethylaminopyridine (0.011 g, 0.091 mmol), triethylamine (0.138 g, 1.36 mmol, 0.19 mL) in dichloromethane (3 mL) was added acetic anhydride (0.185 g, 1.81 mmol, 0.17 mL) and stirred at room temperature for 1 h. Dichloromethane was removed under vacuum, water (5 mL) was added and extracted with ether. Ethereal layers were washed with bicarbonate, brine and dried over anhydrous sodium sulfate. The crude product obtained was purified by flash chromatography (10% ethyl acetate in petroleum ether) to give the acetylated compound 15 (0.145 g, 88%).

IR (CHCl$_3$)   : 3000, 2930, 1725, 1665 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.88-1.99 (m, 2H), 2.02-2.03 (s, 3H),

2.35-2.54 (m, 6H), 4.10-4.14 (t, 2H),

6.79-6.80 (t, 1H).

MS (m/e)   : 182 (M$^+$), 139(M$^+$-C$_2$H$_3$O), 123, 122, 110, 94, 82,

67, 63.

Preparation of heptaldehyde diethyl acetal 16[24]

Hexylmagnesium bromide was prepared from freshly distilled 1-bromohexane (4.127 g, 25 mmol, 3.51 mL) and magnesium powder (0.729 g, 30 mg. atom) in dry ether (30 mL). It was cooled with

ice water and triethyl orthoformate (3.565 g, 24.05 mmol, 4 mL) in dry ether (20 mL) was added to it slowly with stirring. After the addition was over, it was refluxed for six hours and worked up by adding slowly to an excess of saturated aqueous ammonium chloride solution and then extracted with ether. Ether extracts were dried over anhydrous magnesium sulfate, the solvent was evaporated and the crude product was distilled by Kugelrohr distillation assembly to give heptaldehyde diethyl acetate __16__ (3.961 g, 88%) as an oil.

b.p. : 79-81°C/8 mm (lit.[24] b.p. 204-205°C/774 mm).

IR (film) : 2940, 1455, 1370, 1125, 1055 cm^{-1}.

^{1}H NMR (CCl$_4$) : 0.9 (t, 3H, CH$_3$), 1.1 - 1.47 (m, 16H), 3.47 (m, 4H, -OCH$_2$), 4.4 (t, 1H).

Preparation of 1-ethoxy heptene __17__[25a]

Magnesium bromide was prepared from 1,2-dibromoethane (5.25 g, 27.93 mmol, 2.4 mL) and magnesium powder (0.747 g, 30.72 mg. atom) in dry ether (25 mL) under N$_2$. Dry benzene (16 mL) was added and refluxed for 0.5 h to remove the ether. It was cooled to room temperature and triethylamine (2.83 g, 27.93 mmol, 3.9 mL) was added with stirring. After 0.5 h, heptaldehyde diethyl acetal __16__ (3.5 g, 18.62 mmol) in dry benzene (5 mL) was added dropwise and refluxed for 24 h and workedup by carefully adding a saturated ammonium chloride solution and then extracted with ether. Ether extracts were dried over anhydrous potassium carbonate and the solvent was evaporated to yield a residue which was

distilled by Kugelrohr set up to give 1-ethoxy heptene <u>17</u> (1.59 g, 60%) as a colorless oil.

b.p. : 64 - 66°C/20 mm (lit.[25a] b.p. 61°C/16 mm).

IR (thin film) : 3020, 2920, 1650, 1450 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 0.89 (t, 3H, CH$_3$), 1.06-1.34 (m, 9H), 2.06

(m, 2H, allylic), 3.8 (q, 2H, -O-C<u>H</u>$_2$CH$_3$),

4.4 (q, 1H, -C<u>H</u>=CH-O-), 6.0 (d, 1H, -CH=C<u>H</u>-O-).

Preparation of octaldehyde diethyl acetal <u>18</u>

Under similar conditions octaldehyde diethyl acetal was prepared from bromoheptane (7.98 g, 44.55 mmol, 7 mL), magnesium powder (1.216 g, 50 mg atom) and triethyl orthoformate (6.324 g, 42.67 mmol, 7.15 mL) (yield 6.896 g, 80%).

b.p. : 100-105°C/7-8 mm (lit.[25d] b.p. 112-113°C/15mm)

IR (film) : 1460, 1375, 1342, 1130, 1060 cm^{-1}

^{1}H NMR (CDCl$_3$) : 0.9 (t, 3H, CH$_3$), 1.1-1.47 (m, 18H), 3.47

(m, 4H, -OCH$_2$) 4.4 (t, 1H)

Preparation of 1-ethoxy octene <u>19</u>[25e]

Following similar conditions, 1-ethoxy octene <u>19</u> was prepared from magnesium powder (0.37 g, 15.25 mg atom), 1,2-dibromoethane (2.6 g, 13.86 mmol, 1.19 mL), triethylamine (1.403 g, 13.86 mmol, 1.93 mL) and octaldehyde diethyl acetal <u>18</u> (1.334 g, 6.6 mmol) (yield 0.868 g, 65%).

IR (film) : 3020, 2920, 1650, 1460, 1375, 1110 cm^{-1}.

^{1}H NMR (CCl$_4$)   : 0.86 (t, 3H, CH$_3$), 1.15-1.5 (m, 11H, CH$_2$),

2.0 (t, 2H, -CH$_2$-CH=CH), 3.75 (q, 2H, -O-CH$_2$CH$_3$),

4.25 (q, 1H, -CH=CH-O-), 5.85 (d, 1H, -CH=CH-O-).

Oxidation of 1-ethoxy heptene with pyridinium dichromate/t-butyl hydroperoxide

To a stirred solution of pyridinium dichromate (1.20 g, 3.197 mmol) and Celite (1.3 g) in dry benzene (8 mL) was added t-butyl hydroperoxide (0.29 g, 3.197 mmol, 0.31 mL) followed by 1-ethoxy heptene 17 (0.227 g, 1.6 mmol) in dry benzene (2 mL) at 10°C. After 15 min at 10°C, the reaction mixture was stirred for 4 h at 25°C. Ether was added, and the reaction mixture was filtered through a pad of Celite and washed twice with 10 mL portions of ether. The combined filtrate was evaporated, and the residue was purified by flash chromatography (10% ethyl acetate in petroleum ether) to afford ethyl heptanoate 20 (0.107 g, 39%) as an oil.

IR (film)   : 1725 cm^{-1}

^{1}H NMR (CCl$_4$)   : 0.9 (t, 3H, CH$_3$), 1.2-1.4 (br, 11H), 2.75

(t, 2H), 4.25 (q, 2H).

Oxidation of 1-ethoxy octene 19 with pyridinium dichromate/ t-butyl hydroperoxide

Pyridinium dichromate (6.47 g, 17.19 mmol) and Celite (3 g) in benzene (15 mL) were treated with t-butyl hydroperoxide (0.624 g, 6.923 mmol, 0.66 mL) followed by 1-ethoxy octene 19 (0.54 g, 3.46 mmol) in benzene (5 mL) for 4 h at 25°C. The crude product

after purification by chromatography yielded ethyl octanoate $\underline{21}$ (0.12 g, 20%) as an oil.

IR (film)   : 2920, 1725, 1460 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 0.88 (t, 3H), 1.22-1.38 (br, 13H), 2.18 (m, 2H),

4.11-4.36 (q, 2H).

Preparation of 3,4-dihydropyran-2-carboxaldehyde $\underline{22}$[26]

Freshly distilled, acrolein (62.9 g, 1.12 mole, 75 mL) dry benzene (50 mL) and hydroquinone (1.235 g, 0.011 mole) were taken in a steel autoclave and flushed with nitrogen. The reactor was heated gradually to 160°C and maintained at this temperature for 5 h with stirring. The crude reaction product was distilled to give unreacted acrolein (30 g), followed by benzene under reduced pressure. The concentrated crude product was distilled by Kugelrohr distillation assembly to give 3,4-dihydropyran-2-carboxaldehyde $\underline{22}$ (12 g, 18.2%).

b.p.   : 60-62°C/20 mm, (lit.[26b] b.p. 145-148°C/760 mm).

IR (film)   : 3045, 2720, 1730, 1640 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 2.06 (m, 4H), 4.33 (m, 1H), 4.84 (m, 1H),

6.56 (d, 1H), 9.83 (s, 1H).

Preparation of 2-(Z)-1-heptenyl-3,4-dihydro-2H-pyran $\underline{23}$[12]

3,4-Dihydropyran-2-carboxaldehyde $\underline{22}$ (0.595 g, 5.306 mmol) in dry tetrahydrofuran (2 mL) was added dropwise with stirring at 10°C to the ylid generated in situ from hexyltriphenylphosphonium bromide (3.4 g, 7.96 mmol) and n-butyl lithium (0.48 g, 7.43 mmol 4.6 mL) at 10°C under nitrogen. After stirring for 2 h at 10°C,

ether (20 mL) and water (5 mL) were added and the aqueous layer was extracted with ether. The combined extracts were dried over potassium carbonate and solvent evaporated. Petroleum ether (40-60°C) (10 mL) was added and filtered over a cotton plug to remove the separated triphenylphosphine oxide. The petroleum ether layer was concentrated to precipitate solid triphenylphosphine oxide and filtered over a cotton plug. This process was repeated couple of times to remove as much triphenylphosphine oxide as possible to yield the pure the enol ether $\underline{23}^{12}$ (0.678 g, 71%) as a pale yellow oil.

IR (thin film) : 3060, 3010, 2925, 2860, 1640, 1120 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 0.87 (t, 3H), 1.0-2.3 (m, 12H), 4.68 (m, 2H),

5.59 (dd, 2H J=5 Hz), 6.46 (d, 1H, J = 6.25 Hz).

Synthesis of argentilactone $\underline{25}$

Enol ether $\underline{23}$ (0.3 g, 1.67 mmol) in dichloromethane (5 mL) was added dropwise at 0°C to the oxidant generated from pyridinium dichromate (1.253 g, 3.332 mmol) and t-butylhydroperoxide (0.45 g, 4.998 mmol, 0.48 mL). After 4 h the reaction mixture was worked up as before to yield a residue which on chromatographic purification (ethyl acetate : petroleum ether, 1:9) gave the t-butyl peroxy compound $\underline{24}$ (0.110 g, 25%) which was found to be unstable.

IR (neat) : 3000, 2950, 1620, 1200 - 1000 cm^{-1}

On further elution with (1:9, ethyl acetate:petroleum ether) the α,β-unsaturated lactone $\underline{25}^{11-14}$ was obtained (0.130 g, 40%) as an oil.

IR (CHCl$_3$)   : 1720, 1630 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 0.9 (t, 3H), 1.31 (m, 6H), 2.06 (m, 2H), 2.29-

                          2.52 (m, 2H), 5.23-5.78 (m, 3H), 6.06 (dt, 1H),

                          6.92 (dt, 1H).

To a stirred solution of compound <u>24</u> (0.11 g, 0.41 mmol) in toluene (4 mL) was added triethylamine (0.041 g, 0.41 mmol, 0.057 mL) and heated at 60°C for 1 h. The reaction mixture was cooled, water (1 mL) was added and extracted with ether. The ether extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product obtained was purified by flash chromatography to yield the α,β-unsaturated lactone <u>25</u> (0.038 g), which was compared by TLC, IR and ^{1}H NMR and found to be identical to the lactone obtained above.

Preparation of (+)-E-6-(2-phenylvinyl)-3,4-dihydro-2H-Pyran <u>26</u>

3,4-Dihydropyran-2-carboxaldehyde <u>22</u> (1.08 g, 9.63 mmol, 1 mL) in dry tetrahydrofuran (6 mL) and HMPA (0.5 mL) was added dropwise with stirring at 10°C to the ylid generated <u>in situ</u> under nitrogen from benzyl diethylphosphite (3.297 g, 14.45 mmol, 3.06 mL) in tetrahydrofuran (12 mL) and n-butyl lithium (0.925 g, 14.45 mmol, 9.03 mL) at 10°C. After stirring for 2 h at 10°C, ether (25 mL) and water (5 mL) were added and the aqueous layer was extracted with ether. The combined ethereal layers were dried over anhydrous potassium carbonate and the solvent was evaporated. The crude product thus obtained, was purified by column

chromatography over basic alumina (2% ether in petroleum ether) to yield the pure enol ether 26 (0.691 g, 39%).

IR (neat)   : 3050, 3020, 2920, 2840, 1640, 1595 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.59-2.20 (m, 4H), 4.37-4.64 (m, 1H), 4.64-4.86

                    (m, 1H), 6.30 (d, 1H) 6.47 (d, 1H), 6.50

                    (d, 1H, J=15 Hz) 7.09-7.56 (m, 5H).

Synthesis of (±) goniothalamin 27[13,15-19]

Enol ether 26 (0.108 g, 0.581 mmol) in dichloromethane (2 mL) was added dropwise at 0°C to the oxidant generated from pyridinium dichromate (0.437 g, 1.161 mmol) and t-butyl hydroperoxide (0.157 g, 1.74 mmol, 0.17 mL). After 3 h the reaction mixture was worked up as before to yield a residue which on chromatographic purification (4% ethyl acetate in petroleum ether) gave the t-butyl peroxy compound 27a (0.022 g, 14%).

IR (neat)   : 3035, 2980, 2935, 1600, 1100 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.31 (s, 9H), 1.5-1.9 (m, 2H), 4.55-4.86

                    (m, 1H), 6.66 (d, 1H).

Further elution with (ethyl acetate:petroleum ether, 1:9) gave the α,β-unsaturated lactone 27[15] (0.03 g, 26%).

IR (neat)   : 3040, 2930, 1720, 1600, 1250 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.55 (m, 2H), 5.11 (q, 1H), 6.09 (dt, 1H),

                    6.21 (dd, 1H, J = 6.25 and 16.25 Hz) 6.78

                    (d, 1H, J = 16.25 Hz), 6.94 (dt, 1H), 7.38

                    (aromatic, 5H).

MS (m/e)   : 200 (M$^+$), 172, 131, 115, 104, 91, 77.

Conversion of 27a to 27

To a stirred solution of 27a (0.022 g, 0.08 mmol) in toluene (3 mL) was added triethylamine (0.008 g, 0.08 mmol, 0.011 mL) and heated at 80°C for 0.5 h. The reaction mixture was cooled, water (1 mL) was added and extracted with ether. The ether extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product obtained was purified by flash chromatography to yield the α,β-unsaturated lactone 27 (0.011 g), which was compared by TLC, IR and ^{1}H NMR and found to be identical to the lactone obtained above.

Synthesis of (±)-goniothalamin oxide 28

To a stirred solution of goniothalamin 28 (0.1 g, 0.5 mmol) in dichloromethane (10 mL) was added m-chloroperbenzoic acid (0.129 g, 0.747 mmol) and refluxed for 2 h. The reaction mixture was cooled and saturated sodium bicarbonate solution (10 mL) was added and the layers were seperated. The aqueous layer was extracted with dichloromethane (15 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The crude product obtained on evaporation of the solvent was purified by flash chromatography (ethyl acetate : petroleum ether, 1:9) afforded 28 (0.08 g, 74%) as a solid.

m.p : 91-92°c (lit[18] m.p. 90-94°C).

IR (KBr) : 3040, 2980, 1720, 1250, 1040 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.55 (m, 2H), 3.25 (dd, 1H, J=1.8 and 5.4 Hz)

3.86 (d, 1H, J=1.8 Hz), 4.48 (dt, 1H, J=5.4

and 7.4 Hz), 6.03 (dt, 1H, J=1.6 and 9.5 Hz)

6.92 (dt, 1H, J=4.7 and 9.5 Hz), 7.3 (br s, 5H).

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I.3   FACILE AND SELECTIVE DEOXIMATION OF KETOXIMES

I.3.a Introduction

Regeneration of carbonyl compounds from its derivatives under mild conditions is an important process in synthetic organic chemistry.   Many methods have been reported in the literature for the oxidative cleavage of oximes, 2,4-dinitrophenyl hydrazones and N,N-dimethyl hydrazones to their parent carbonyl compounds.

Hershberg et al[1] reported for the first time deoximation reactions under acidic conditions.   However, this methodology can not be used for substrates containing acid sensitive functional groups.

Lead tetra acetate[2] has been found to be a general reagent for deoximation reactions.   The order of yields are aliphatic aldoximes > aliphatic ketoximes > alicyclic ketoximes > aromatic ketoximes.   Quantitative evolution of nitrogen was seen in each case.   However, camphoroxime did not undergo any appreciable reaction under similar conditions.   Another drawback encountered in the case of o- and p-hydroxy acetophenone and vanillinoxime is that, these oximes destroy lead tetraacetate and the starting material is recovered unchanged.Bird and coworkers[3] reported deoximation with ceric ammonium nitrate in aqueous alcohol, acetonitrile and / or acetic acid.

Mahajan et al[4] have reported the deoximation of a number of ketoximes by treatment with chromium trioxide/sulfuric acid (Jones' reagent), chromium trioxide / pyridine and periodic acid. A comparative study of these three reagents were carried out. Treatment with periodic acid in ether and acetic acid usually gave good results but the process was marred by the liberation of iodine and occasional formation of iodinated products. Some side reactions also were observed and nitro compounds were detected as by products.

Taylor and coworkers[5] treated oximes of aldehydes and ketones with thallium(III) nitrate (TTN) in methanol. The reaction was rapid. Although this method proceeds virtually instantaneously at room temperature, it is unsuccessful when applied to aryl aldehydes and ketones having o- and p-hydroxy and amino groups. Oximes with isolated carbon-carbon double bonds undergo deoximation and oxidative rearrangements leading to mixture of products.

Pyridinium chlorochromate[6] in dichloromethane has been used for deoximation. This reaction requires greater than 12 h at room temperature and benzaldoxime was converted to benzaldehyde with some over oxidation.

Drabowicz[7] has reported that deoximation can be carried out using with PCC and hydrogen peroxide which proceeds within minutes at $0^{\circ}-10^{\circ}C$. Over oxidation of benzaldehyde is again a drawback.

Olah et al[8] have reported oxidative cleavage of ketoximes with aqueous bromine. It is probable that sodium hypobromite is the reagent for oxidative cleavage. However, oxidative cleavage of aldoximes under these reaction conditions are accompained by other side products.

Benzene seleninic anhydride has been found to be a useful reagent for deoximation by Barton.[9] Depuy[10] has shown that levulinic acid is an excellent reagent for hydrolysis of oximes and 2,4-dinitrophenyl hydrazones.

Satish and Kalyanam[11] have reported the regeneration of carbonyl compounds in good yields from oximes using PDC at room temperature.

It has recently been shown from our laboratories[12] that cetyltrimethylammonium permanganate (CTAP) oxidatively cleaves oximes, 2,4-dinitrophenyl hydrazones and N,N-dimethyl hydrazones to the corresponding carbonyl compounds in high yields and in short period of time.

Selective deoximation of aldoximes by PCC in the presence of DCC has been reported by Bhaduri et al[13]. Kim and coworkers have demonstrated the use of dinitrogen tetroxide for the deoximation of dialkyl or aryl alkyl oximes at -40°C in good yields.[14]

Recently ion exchange resins Dowex-50[15] and Amberlyst-15[16] have been used for the efficient regeneration of carbonyl compounds from oximes and semicarbazones.

I.3.b. Results and Discussion
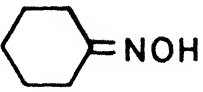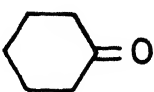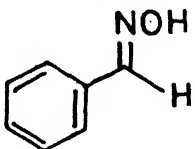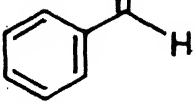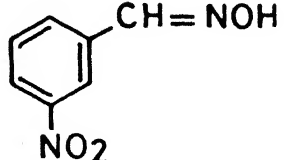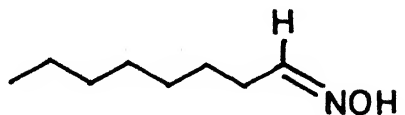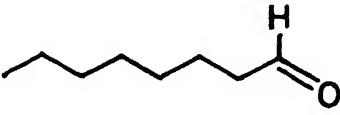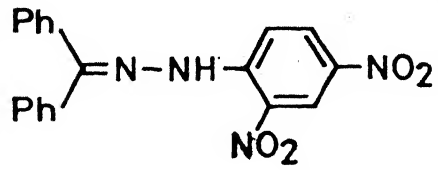
In the course of our studies on oxidation with this new reagent system, PDC/t-BuOOH, we explored the usefulness of this reagent for other organic transformations. It has now been found that PDC/t-BuOOH is a convenient and highly selective reagent for the deoximation of ketoximes in preference to aldoximes. Thus treatment of a variety of ketoximes with four equivalents of PDC/t-BuOOH at $0°C$ for 2.5-4.5 h yielded the corresponding carbonyl compounds in high yields. The usefulness of this methodology is illustrated with a number of examples (Table - I.C.1). There are a few cases which are of particular interest.

This reagent system PDC/t-BuOOH has earlier been shown to be a good reagent for effecting allylic and benzylic oxidations (Chapter - I. 1). However ketoximes 7 and 9 having benzylic carbons underwent deoximation preferentially in high yield without any benzylic oxidation. Similarly, ketoximes 11 and 13 afforded the corresponding carbonyl compounds without any allylic oxidation. On the other hand the order of reactivity and hence the selectivity that one achieves in the reaction of aldoximes is remarkable. For example, benzaldoxime 17 on treatment with PDC/ t-BuOOH under the usual reaction conditions (3 h) underwent deoximation only to the extent of ~5% and most of the aldoxime could be recovered unchanged. Even after treatment with an excess of reagent and longer reaction time (45 h) deoximation occured only to the extent of ~28%. m-Nitrobenzaldoxime 19 on

TABLE I.C.1

Entry	Substrate	Time, h	Product	Yield (%
1	(1) acetophenone oxime	3	(2) acetophenone	92
2	(3) 4-bromoacetophenone oxime	2.5	(4) 4-bromoacetophenone	80
3	(5) benzophenone oxime (Ph₂C=NOH)	4.5	(6) benzophenone (Ph₂C=O)	98
4	(7) deoxybenzoin oxime (Ph-C(=NOH)-CH₂-Ph)	4	(8) deoxybenzoin (Ph-CO-CH₂-Ph)	81
5	(9) 4-phenyl-2-butanone oxime (Ph-CH₂CH₂-C(=NOH)-CH₃)	3.5	(10) 4-phenyl-2-butanone	71
6	(11)	4.5	(12)	80
7	(13)	4	(14)	95

Entry	Substrate	Time, h	Product	Yield(%)
8	(cyclohexanone oxime) =NOH **15**	2.5	(cyclohexanone) =O **16**	92
9	(benzaldoxime) NOH / H **17**	3	(benzaldehyde) O / H **18**	~5
		45	**18**	28
10	CH=NOH / NO₂ **19**	24	No reaction	–
11	(octanal oxime) H / NOH **20**	4.5	(octanal) H / O **21**	9
12	Ph / Ph =N–NH–(2,4-dinitrophenyl) NO₂, NO₂ **22**	36	No reaction	–

treatment with PDC/t-BuOOH for 24 h did not show any appreciable reaction. A similar trend was observed even in the reaction of aldoximes derived from aliphatic aldehydes. Thus more than 90% of aldoxime 20 could be recovered unchanged after treatment with the oxidising agent for 4.5 h. Thus it is clear that using this reagent system it would be possible to deprotect ketoximes in the presence of aldoximes. Most of the reagents available in the literature for effecting deoximation would not be able to offer a selectivity of this type. It is also interesting to note that 2,4-dinitrophenylhydrazones are generally inert to this reagent system (22, Table - I.C.1). A number of methods of oxidative cleavage of C=N bond of oximes also affect the C=N bond of 2,4-dinitrophenyl hydrazones. Here again the present methodology offers scope for exploitation in organic synthesis.

With these experimental observations at hand, we have postulated a mechanism for deoximation with our perchromate reagent PDC/t-BuOOH (Scheme I.C.1). Although this mechanism is speculative, it has similarities to the one envisioned for Cerium(IV)[4] and Chromium(VI)[15] mediated deoximation reaction reported in the literature. The first step involves one electron oxidation (similar to Ce(IV)) of the oxime by hydrogen atom abstraction to produce the radical 23. Further reaction with chromium(VI) reagent can form the chromate ester 24. Hydrolysis of 24 then yields the carbonyl compound via intermediate 25.[4] It is possible that the formation of a more stable radical 14 is facile in

SCHEME I.C.1
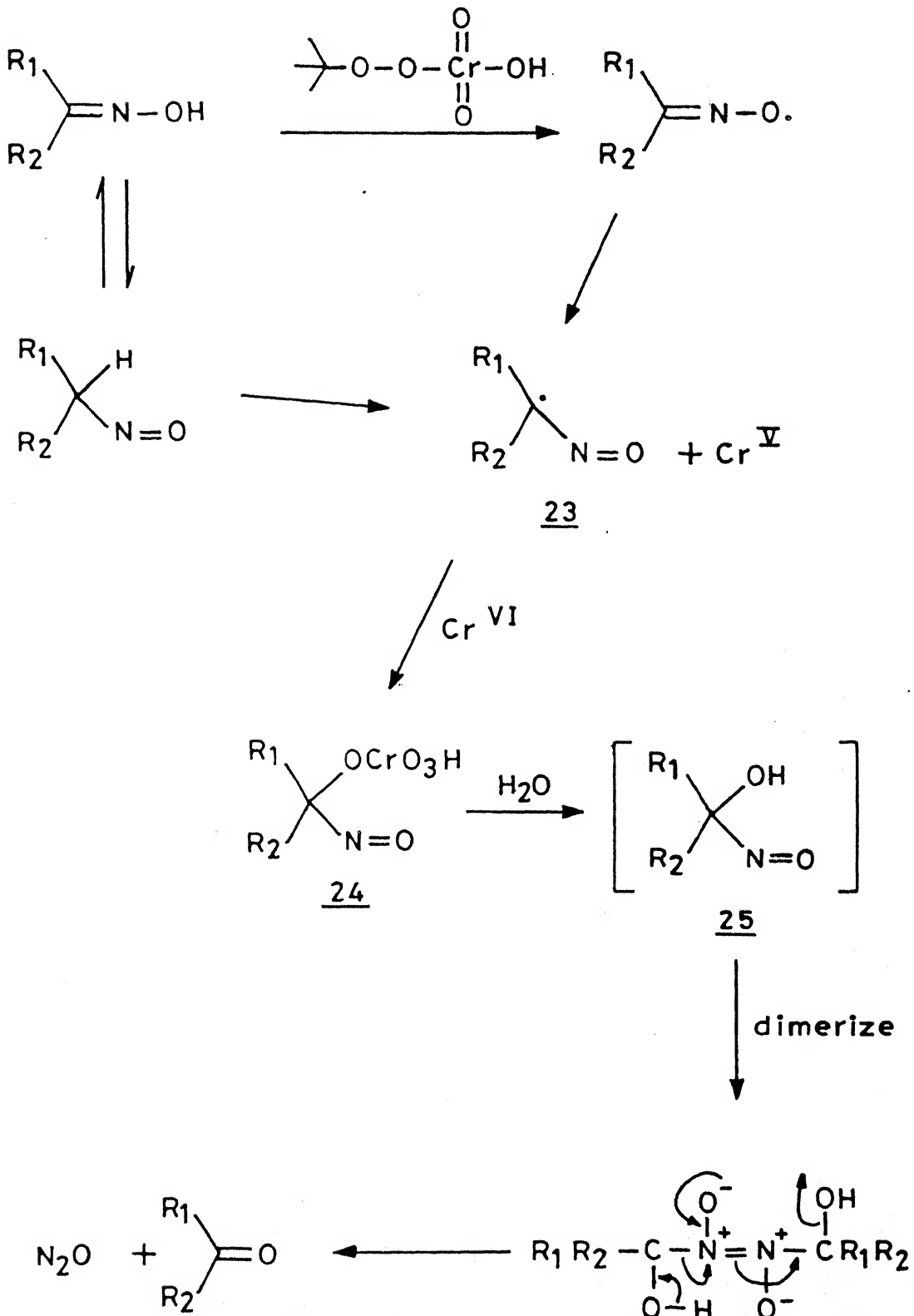
the case of ketoximes than aldoximes and hence the observed selectivity.

I.3.c Experimental

General Procedures

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, tlc, m.p.).

Materials

Commercial grade solvents were distilled prior to use. Pyridine was distilled over potassium hydroxide pellets. Chromium trioxide flakes (BDH, E. Merck) and 70% t-butyl hydroperoxide (Koch Light Laboratories Ltd.) were used as such. Octanaloxime was prepared following the reported procedure.[17] Pyridinium dichromate was prepared according to the procedure mentioned in Chapter I.1. Petroleum ether fractions 60-80°C were used for chromatography.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) Ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of

phosphomolybdic acid in ethanol followed by heating to ca. 200°C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and then reimmersion and heating to ca. 200°C.

Column chromatography was performed using 100-200 mesh Acme silica gel. Flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical data

Melting points (m.p.) were determined with a Uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Bulb to bulb distillation was carried out using Büchi GKR-50 distillation unit.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80 instrument. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), etc.

General procedure for the preparation of oximes[18]

A mixture of the carbonyl compound (0.5 g), hydroxylamine hydrochloride (0.5 g) and pyridine (0.5 mL) were refluxed in ethanol (5 mL) for 1 h. Ethanol was removed under vacuum. Water (5 mL) was added to the cooled residue and stirred until the oxime crystallized. The solid was filtered over a Buchner funnel, washed with water (5 mL) and dried. The crude compound thus obtained was recrystallized from ethanol to afford the oxime.

General procedure for the regeneration of carbonyl compounds from oximes

The oxidant was generated in solution by treating pyridinium dichromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (7.5 mL) for 15 min at $0^{\circ}C$. The dichloromethane layer was filtered over a cotton plug into another round bottomed flask kept at $0^{\circ}C$. The reagent flask was rinsed with dichloromethane (2.5 mL) and filtered. To this, the carbonyl derivative (oxime) (1 mmol) in dichloromethane (2 mL) was added dropwise and the reaction mixture was stirred at $0^{\circ}C$ for 2 h and then allowed to come to room temperature over a period of another 2 h. Dichloromethane was removed under vacuum and ether (15 mL) was added and filtered over a pad of Celite and the solvent was evaporated. The crude product was purified by flash chromatography (ethyl acetate : petroleum ether, 1 : 9) to give the carbonyl compound, which was found to be identical with an authentic sample.

82

Oxidative cleavage of acetophenoneoxime 1

Acetophenoneoxime 1 (0.135 g, 1 mmol) with pyridinium di-chromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane under similar reaction conditions (3 h) gave acetophenone 2 (0.111 g, 92%).

Oxidative cleavage of 4-bromo acetophenoneoxime 3

4-Bromo acetophenoneoxime 3 (0.214 g, 1 mmol), pyridinium dichromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (12 mL) under similar reaction conditions (2.5 h) gave 4-bromo acetophenone 4 (0.160 g, 80%). m.p. : 49-51°C (lit.[19] m.p. 51°C).

Oxidative cleavage of benzophenoneoxime 5

Benzophenoneoxime 5 (0.197 g, 1 mmol), pyridinium dichromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (12 mL) under similar reaction conditions (4.5 h) gave benzophenone 6 (0.178 g, 98%). m.p. : 48-50°C (lit.[19] m.p. 49-51°C).

Oxidative cleavage of 1,2-diphenylethanoneoxime 7

1,2-Diphenylethanoneoxime 7 (0.105 g, 0.5 mmol), pyridinium dichromate (0.752 g, 2 mmol) and t-butyl hydroperoxide (0.18 g, 2 mmol, 0.19 mL) in dichloromethane (5 mL) under similar reaction conditions (4 h) gave 1,2-diphenyl ethanone 8 (0.073 g, 81%). m.p. : 58-60°C (lit.[19] m.p. 60°C).

Oxidative cleavage of 4-phenyl butan-2-oneoxime 9

    4-Phenyl butan-2-oneoxime 9 (0.163 g, 1 mmol), pyridinium dichromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (10 mL) under similar reaction conditions (3.5 h) gave 4-phenyl butan-2-one 10 (0.105 g, 71%), 2,4-DNP m.p. 131-132°C.

Oxidative cleavage of 6-methyl hept-5-en-2-oneoxime 11

    6-Methyl hept-5-en-2-oneoxime 11 (0.141 g, 1 mmol), pyridinium dichromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (12 mL) under similar reaction conditions (4.5 h) gave 6-methyl hept-5-en-2-one 12 (0.101 g, 80%).

IR (neat)   : 2960, 2900, 1710, 1670 cm^{-1}.

^{1}H NMR (CCl$_4$)   : 1.5 (s, 3H), 1.6 (s, 3H), 2.0 (s, 3H), 2.1-2.5 (m, 4H), 5.0 (t, 1H).

Oxidative cleavage of hex-5-en-2-oneoxime 13

    Hex-5-en-2-oneoxime 13 (0.139 g, 1.23 mmol), pyridinium dichromate (1.851 g, 4.92 mmol) and t-butyl hydroperoxide (0.443 g, 4.92 mmol, 0.47 mL) in dichloromethane (8 mL) under similar reaction conditions (4 h) gave hex-5-en-2-one 14 (0.115 g, 95%).

IR (neat)   : 3080, 1715, 1640 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 2.14 (s, 3H), 2.24-2.64 (m, 4H), 4.9-5.14 (m, 2H), 5.6-6.04 (m, 1H).

Oxidative cleavage of cyclohexanone oxime <u>15</u>

Cyclohexanoneoxime <u>15</u> (0.113 g, 1 mmol), pyridinium dichro-mate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (8 mL) under similar reaction condi-tions (2.5 h) gave the crude product which on distillation by Kugelrohr distillation assembly gave cyclohexanone <u>16</u> (0.090 g, 92%), 2,4-DNP m.p. 160-162°C.

Oxidative cleavage of benzaldoxime <u>17</u>

Benzaldoxime <u>17</u> (0.121 g, 1 mmol), pyridinium dichromate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (10 mL) under similar reaction conditions (4.5 h) gave benzaldehyde <u>18</u> (0.030 g, 28.3%) and unreacted benzaldoxime <u>17</u> (0.074 g, 61.2%).

m.p.   : 34-35°C.

Reaction of m-nitrobenzaldoxime <u>19</u> with PDC/t-BuOOH

m-Nitrobenzaldoxime <u>19</u> (0.166 g, 1 mmol), pyridinium dichro-mate (1.505 g, 4 mmol) and t-butyl hydroperoxide (0.36 g, 4 mmol, 0.38 mL) in dichloromethane (12 mL) under similar conditions (24 h) did not undergo oxidative cleavage. The starting material was recovered unchanged.

Oxidative cleavage of octanaloxime <u>20</u>

Octanaloxime <u>20</u> (0.072 g, 0.5 mmol), pyridinium dichromate (0.752 g, 2 mmol) and t-butyl hydroperoxide (0.18 g, 2 mmol, 0.19 mL) were reacted in dichloromethane (6 mL) under similar reaction conditions for 4.5 h. The crude reaction product thus obtained

on analysis by Iatroscan TH-10 analyser showed the conversion to octanal <u>21</u> (9%).

Reaction of 2,4-DNP derivative of benzophenone <u>22</u> with PDC/t-BuOOH

2,4-DNP derivative of benzopnenone <u>22</u> (0.193 g, 0.5 mmol), pyridinium dichromate (0.752 g, 2 mmol) and t-butyl hydroperoxide (0.18 g, 2 mmol, 0.19 mL) in dichloromethane (10 mL) under similar reaction conditions (36 h) did not undergo oxidative cleavage and the starting material was recovered unchanged.

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Part-B REACTION OF ALLYLIC AND BENZYLIC ESTERS WITH LOW VALENT
TITANIUM REAGENTS

I.4.a   Introduction

Protection   of   a sensitive functional group in   a   multi-
functional   molecule   for   carrying   out   a   selective   chemical
transformation   and its subsequent deblocking under   mild   condi-
tions   forms   an integral unit in any organic chemist's synthetic
methodology.   An   essential   requisite for such   protection   and
deprotection   is that the protecting group as well as the   depro-
tecting   agent must be non-toxic and at the same time   leave   the
other functional groups in the molecule unaffected.

Carboxylic   acids are normally protected as their   allylic
and benzylic esters.   Although many methods are available for de-
protection of esters,[1] very few methods are at hand for their non
saponificative hydrolysis.   Among the various methods   available
for   hydrolysis include specific deblocking of cinnamyl esters by
Corey   and   Tius   using successive methoxy   mercuration   and   de-
mercurio carboxylation procedure.[2]   Allylic   esters   have   been
cleaved   with   lithium   dimethyl   cuprate.[3]   The   commonly   used
methods   for   the cleavage of benzylic esters are   hydrogenolysis
with palladium on carbon[4], hydrolysis with potassium carbonate in
water-tetrahydrofuran[5] and nitrosonium hexafluorophosphate[6].   Na
in   liquid   ammonia   had also been used for   the   same   purpose[7].
Benzylic   esters   of   penicillin derivatives   were   cleaved   with
aluminium chloride[8].   Recently chromium trioxide /chlorotrimethyl
silane   has   been used to oxidatively   cleave   benzylic   esters.[9]

Although these reagents are good in their own way for deprotection, there exists always a need for developing a reagent to deprotect under milder conditions. Owing to the limited availability of reagents for specific transformations, new reagents were and are continued to be developed.

Transition metal mediated organic reactions are known for some time, but their increasing utility for selective functional group transformations was realised only recently. Literature on transition metal mediated diverse organic transformations are in plenty and they are also being used in asymmetric synthesis.[10]
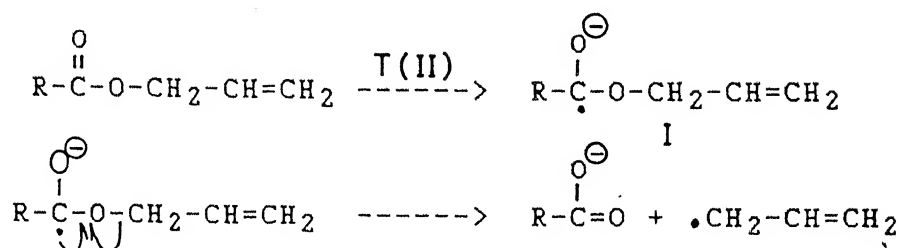
Low valent titanium species were generated either by the reduction of $TiCl_3/LiAlH_4$[11] or by the reduction of $TiCl_4/Mg$-Hg[12] and have been used for the intramolecular and intermolecular pinacolic coupling of carbonyl compounds to give olefins[11] and pinacols[12] in excellent yields.

Earlier work from our laboratory on low valent titanium reagents for the synthesis of Karahanaenone via the formation of pinacols from unsymmetrical ketones[13] and for the mild reduction of nitro compounds to amines in excellent yields[14] prompted us to study the reactivity of this titanium(II) reagent towards allylic and benzylic esters.
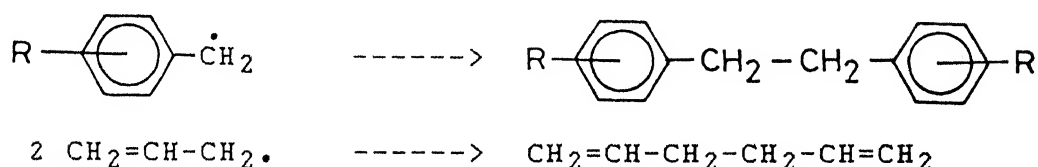
These reductions and reductive coupling reactions are expected to proceed via electron transfer mechanism. Based on this it seemed reasonable to visualise the intermediacy of radical anions of the type 1 for allylic and benzylic esters, which would then

be expected to undergo homolytic fission to yield the carboxylate anion and allyl/benzyl radical which ultimately would combine to give biallyl/bibenzyl as shown below (Scheme I. D. 1).

SCHEME I. D. 1

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2-CH=CH_2 \xrightarrow{\quad T(II) \quad} R-\overset{\overset{\displaystyle O^{\ominus}}{|}}{\underset{\displaystyle \bullet}{C}}-O-CH_2-CH=CH_2$$

I

$$R-\overset{\overset{\displaystyle O^{\ominus}}{|}}{C}-O-CH_2-CH=CH_2 \xrightarrow{\quad\quad} R-C=O + \bullet CH_2-CH=CH_2$$

Similarly

$$2\ CH_2=CH-CH_2\bullet \xrightarrow{\quad\quad} CH_2=CH-CH_2-CH_2-CH=CH_2$$

It was of interest to study whether allylic and benzylic esters would undergo reductive cleavage with low valent titanium reagents under mild reaction conditions to yield carboxylic acids. In the event, it would turn out to be a reasonable way to deprotect allylic and benzylic esters. The results obtained in such a study are reported in this chapter.
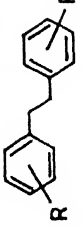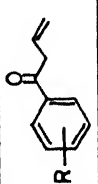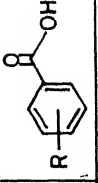
I.4.b Results and Discussion
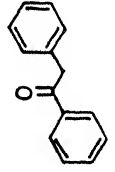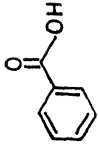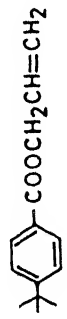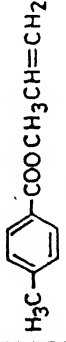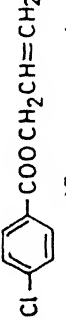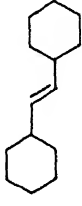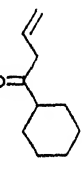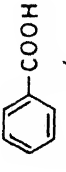
It was anticipated that allylic and benzylic esters would undergo reductive cleavage readily with titanium(II) reagent derived from titanium tetrachloride and amalgamated magnesium. The driving force for such a pathway would be the formation of a carboxylate anion and a stable allylic/benzylic radical from the initially formed radical anionic species (Scheme I. D. 1)

With this in mind, we carried out the reductive cleavage of a number of allylic/benzylic esters with $TiCl_4$/Mg-Hg. The results of these reactions are summarised in Table - I. D. 1. In a typical example benzyl benzoate (2 eq.) was added to the Ti(II) species generated at $0°C$ from titanium tetrachloride (4 eq) and amalgamated magnesium (10 eq) in anhydrous tetrahydrofuran and stirred for 2 h by which time the reaction was allowed to raise to room temperature. As expected benzoic acid $\underline{4}$ was obtained as a major product (64%). Chromatographic purification of the neutral material yielded dibenzyl $\underline{2}$[15] (18%) and the ketone $\underline{3}$[16] (14%). Treatment of allyl benzoate $\underline{5}$ under the same reaction conditions afforded benzoic acid $\underline{4}$ (41%) phenyl allyl ketone $\underline{6}$[17,22] (21%) and dibenzyl $\underline{2}$[15] (29%).

The allyl ester $\underline{7}$ under similar conditions gave the acid $\underline{10}$ (32%), the ketone $\underline{9}$[18] (19%) and the dimeric hydrocarbon $\underline{8}$[15] (19%) In the case of three other allylic esters $\underline{11}$, $\underline{15}$ and $\underline{19}$, the corresponding carboxylic acids were isolated as the major products along with the formation of the corresponding allyl ketones and the dimeric hydrocarbons. The neutral products obtained in these reactions were characterised by comparison with authentic samples and by IR, ^{1}H-NMR and mass spectral data.

These results, together with the particular efficiency with which ester of benzylic and allylic alcohols are reduced, lead us to favour a mechanism involving fragmentation of the initially

TABLE I.D.1

Entry	Substrate	Yield (%)	Yield (%)	Yield (%)
1	COOCH_2-phenyl **1**	**2** 18	**3** 14	**4** 64
2	$\text{COOCH}_2\text{CH=CH}_2$-phenyl **5**	**2** 29	**6** 21	**4** 41
3	t-Bu-phenyl-$\text{COOCH}_2\text{CH=CH}_2$ **7**	**8** 19	**9** 19	**10** 32
4	H_3C-phenyl-$\text{COOCH}_3\text{CH=CH}_2$ **11**	**12** 18	**13** 22	**14** 49
5	Cl-phenyl-$\text{COOCH}_2\text{CH=CH}_2$ **15**	**16** 20	**17** 22	**18** 26
6	Cl-phenyl-$\text{COOCH}_2\text{CH=CH}_2$ **19**	**20** 17	**21** 25	**22** 26
7	cyclohexyl-$\text{COOCH}_2\text{CH=CH}_2$ **23**	**24** 17	**25** 15	**26** 21
8	phenyl-COOH **4**	**2** 12		

formed radical anion (Scheme I.D.2). Path (a) and thence deoxygenation evidently becomes a favoured process when cleavage of this C-O bond results in the formation of carboxylic acid and the stable allylic or benzylic radical. When path (b) is operative some alcohol is regenerated and the benzoyl radical is formed. Coupling of the benzoyl and allyl radicals can lead to the allyl phenyl ketone.

$$Scheme - I. D. 2$$
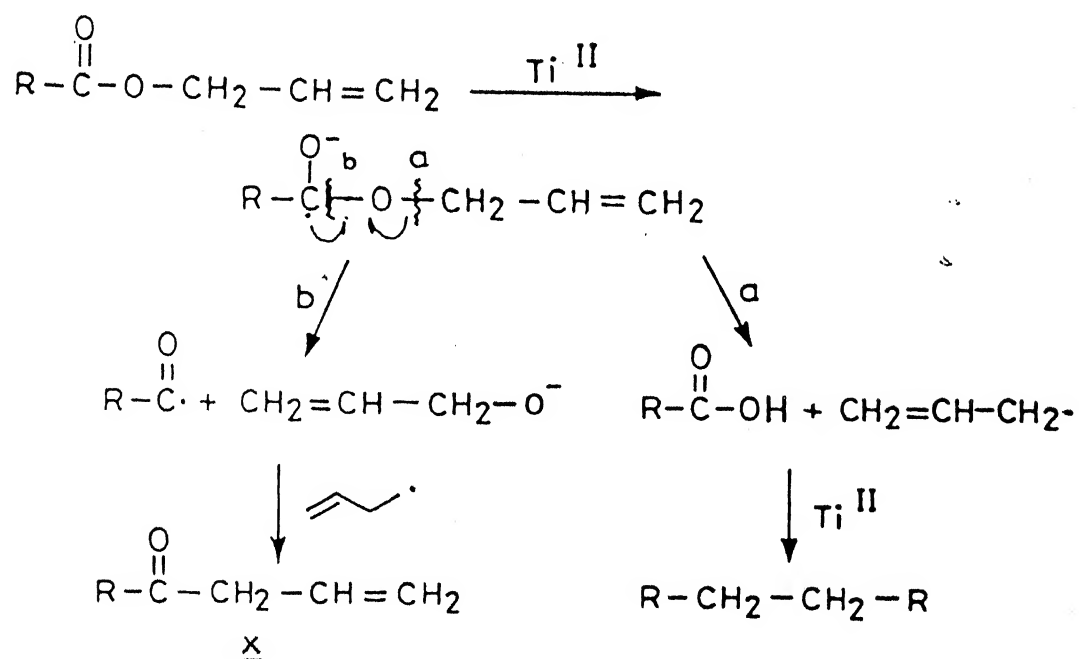
It appears that one pathway available for the formation of dibenzyl derivatives can be from the carboxylic acids. This has been found to be true when benzoic acid 4 was treated with $TiCl_4$/ Mg-Hg under the same reaction condition dibenzyl 2 was isolated as one of the products of the reaction in 12% yield. The mechanism postulated for the reductive cleavage of allylic esters of carboxylic acids is similar to the one proposed by Barton[19] for

the deoxygenation of sterically hindered esters with Li/ethyl-amine. The formation of ketones similar to $\underline{X}$ has been reported by Tochtermann[20] in the reductive cleavage of benzhydryl benzo-ates with lithium naphthalenide.

I.4.c Experimental

General Procedures

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, tlc, m.p.).

Materials

Commercial grade solvents were distilled prior to use. Tetrahydrofuran (THF) was dried over potassium hydroxide, distil-led over sodium wire and kept over sodium wire. It was further distilled over lithium aluminium hydride prior to use. Benzyl benzoate (BDH) was distilled prior to use. Titanium tetrachlo-ride was obtained from (Riedel) and used as such. Petroleum ether fractions $60-80^{\circ}C$ were used for chromatography.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) Ultraviolet illumination; (b) exposure

to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to <u>ca</u>. 200°C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and then reimmersion and heating to <u>ca</u>. 200°C.

Column chromatography was performed using 100-200 mesh Acme silica gel. Flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical data

Melting points (m.p.) were determined with a Uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Bulb to bulb distillation was carried out on a Büchi GKR-50 distillation apparatus.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80 instrument. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet),

br (broad), etc. Coupling constants are reported wherever necessary and are expressed in Hz. Mass spectra (MS) were recorded on a Jeol JMS- D 300 mass spectrometer. Principal molecular fragments are reported.

General method for the preparation of allyl esters[21]

Carboxylic acid (1 equiv), allyl alcohol (5 equiv), conc. sulfuric acid (1 mL) were taken in a (25 mL) round bottomed flask and refluxed for 4 hrs. After monitoring by TLC, water was carefully added and extracted with ether. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were successively washed with water, bicarbonate solution, brine and dried over anhydrous sodium sulfate. The crude product obtained after evaporation of the solvent was distilled by Kugelrohr distillation assembly to give the pure allyl ester.

Preparation of allyl benzoate 5[21]

Benzoic acid 4 (5 g, 41 mmol), allyl alcohol (11.9 g, 205 mmol, 14 mL) and conc. sulfuric acid (2 mL) were treated under similar reaction conditions to afford allyl benzoate 5 (4.8 g, 72%).

b.p.   : 93-95°C/4 mm (lit.[21] b.p. 230°C/760 mm).

IR (neat)   : 3060, 3020, 2940, 1730, 1640, 1600 cm^{-1}

^{1}H NMR (CCl$_4$) : 4.53 (d, 2H), 5.13-5.33 (t, 2H), 5.73-5.93

              (m, 1H), 7.26 (s, 5H).

Preparation of allyl-4-t-butylbenzoate 7

4-t-butylbenzoic acid 10 (5 g, 28.05 mmol) allyl alcohol (8.147 g, 140 mmol, 9.54 mL) and conc. sulfuric acid (1 mL) were treated under similar conditions to give allyl-4-t-butylbenzoate 7 (3.5 g, 57%).

b.p.   : 150°C / 17 mm.

IR (neat)   : 3080, 2960, 1720, 1650, 1610 cm^{-1}.

^{1}H NMR (CCl$_4$) : 1.28 (s, 9H), 4.71 (d, 2H), 5.12-5.53 (m, 2H),

5.71-6.34 (m, 1H), 7.43 (d, 2H), 8.0 (d, 2H).

Preparation of allyl-p-toluate 11

p-Toluic acid 14 (5 g, 37 mmol), allyl alcohol (10.66 g, 184 mmol, 12.5 mL) and conc. sulfuric acid (1 mL) were treated under similar conditions to give allyl-p-toluate 11 (5 g, 77%).

IR (neat)   : 3080, 3020, 2950, 1720, 1650, 1580 cm^{-1}.

^{1}H NMR (CCl$_4$) : 2.33 (s, 3H), 4.63 (d, 2H), 5.0-5.4 (m, 2H)

5.6-6.2 (m, 1H), 6.96 (d, 2H), 7.73 (d, 2H).

Preparation of allyl-4-chlorobenzoate 15

4-Chlorobenzoic acid 18 (5 g, 32 mmol), allyl alcohol (8.7 g 150 mmol, 10 mL) and conc. sulfuric acid (1 mL) were treated under similar conditions to give allyl-4-chloro benzoate 15 (4.0 g, 64%).

b.p.   : 120°C / 16 mm.

IR (neat)   : 3080, 3040, 2940, 1725, 1615 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 4.76 (d, 2H), 5.15-5.56 (m, 2H), 5.78-6.40

(m, 1H), 7.46 (d, 2H), 8.06 (d, 2H).

Preparation of allyl-3-chlorobenzoate <u>19</u>

m-Chlorobenzoic acid <u>22</u> (5 g, 32 mmol), allyl alcohol (8.7 g, 150 mmol, 10 mL) and conc. sulfuric acid (1 mL) were treated under similar reaction conditions to afford allyl-3-chloro-benzoate <u>19</u> (5 g, 80%).

IR (neat)   : 3080, 3040, 1720, 1650, 1615 cm^{-1}.

^{1}H NMR (CCl$_4$)   : 4.66 (d, 2H), 5.0-5.43 (m, 2H), 5.6-6.2 (m, 1H), 7.06-7.33 (m, 2H), 7.60-7.86 (m, 2H).

Preparation of allyl cyclohexylcarboxylate <u>23</u>

Cyclohexylcarboxylic acid <u>26</u> (5 g, 39 mmol), allyl alcohol (11.34 g, 195 mmol, 13 mL) and conc. sulfuric acid (1 mL) were treated under similar conditions to give allyl cyclohexyl carboxylate <u>23</u> (4.95 g, 75%).

b.p.   : 85°C / 15 mm.

IR(neat)   : 3080, 2940, 2860, 1730, 1650 cm^{-1}.

^{1}H NMR (CCl$_4$)   : 1.13-2.13 (br m, 10H), 2.3 (s, 1H), 4.50 (d, 2H), 5.12-5.50 (m, 2H), 5.7-6.36 (m, 1H).

General procedure for the reductive cleavage of allylic and benzylic esters with low valent titanium reagents

Reaction of Benzyl benzoate <u>1</u> with TiCl$_4$/Mg-Hg

To a solution of mercuric chloride (0.243 g, 0.90 mmol) in anhydrous tetrahydrofuran (10 mL) was added magnesium powder (0.72 g, 30 mg atom) and the resulting mixture was stirred at room temperature under nitrogen atmosphere for 0.25 h. The

turbid supernatant liquid was withdrawn by syringe and the amalgam was washed with three portions (5 mL) of tetrahydrofuran. The reaction mixture was cooled to $0^{o}C$ after adding tetrahydrofuran (20 mL). Titanium tetrachloride (2.267 g, 12 mmol, 1.31 mL) was added dropwise. The walls of the reaction flask were washed with THF (10 mL) and a solution of benzyl benzoate 1 (1.272 g, 6 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was stirred for 2 h at $0^{o}C$ and then treated with 10% aqueous potassium carbonate solution (10 mL) and stirred for 10 minutes. Chloroform (25 mL) was added and the mixture was filtered through a pad of Celite and sand layers, packed alternatively. The layers were separated and the aqueous layer was extracted with two portions (25 mL) of chloroform. The organic layers were combined and washed with saturated sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product thus obtained was purified by flash chromatography (elution with petroleum ether) to yield the hydrocarbon dibenzyl 2 (0.2 g, 18%).

m.p : $50-52^{o}C$ (lit.[21] $52^{o}C$)

IR (KBr) : 3060, 3020, 2920, 1600 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.83 (s, 4H), 7.19 (s, 10H).

Further elution with (5% ethyl acetate in petroleum ether) gave benzyl benzophenone 3[16] (0.165 g, 14%) as a solid.

m.p. : $58-59^{o}C$ (lit.[16] m.p. $60^{o}C$).

IR (KBr)   : 3080, 3060, 1690, 1610, 1590 cm^{-1}.

^{1}H NMR   : 4.1 (s, 2H), 7.2 (s, 5H), 7.4 (m, 3H),

                    7.9 (m, 2H).

The bicarbonate layer was neutralised at 0°C with 10% hydrochloric acid and extracted with three portions (25 mL) of chloroform and dried over anhydrous sodium sulfate. The solvent was evaporated to afford benzoic acid **4** (0.472 g, 64%).

m.p   : 120-122°C (lit.[21] m.p. 120-122°C)

Reductive cleavage of allyl benzoate **5**

Allyl benzoate **5** (0.324 g, 2 mmol) in tetrahydrofuran (5 mL) was added to the titanium(II) reagent generated _in situ_ at 0°C from titanium tetrachloride (0.759 g, 4 mmol, 0.44 mL), magnesium powder (0.243 g, 10 mg atom) and mercuric chloride (0.081 g, 0.30 mmol). Following similar reaction conditions (2 h) yielded benzoic acid **4** (0.100 g, 41%), dibenzyl **2** (0.07 g, 29%) and allyl phenyl ketone[17,22] **6** (0.060 g, 21%).

The spectral data for dibenzyl **2** are as follows :

m.p   : 49-51°C (lit.[21] m.p. 52°C)

IR (KBr)   : 3040, 3000, 2900, 1600 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.9 (s, 4H), 7.28 (s, 10H).

The spectral data for allyl phenyl ketone **6**[17,22] are as follows:

IR (neat)   : 3060, 3020, 2920, 1680, 1640, 1600 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.67 (t, 2H), 5.25 (d, 2H), 5.7-6.0 (m, 1H),

                    7.45 (br m, 5H).

Ms (m/e)   : 146(M^{+}), 105, 91, 77.

Reductive cleavage of allyl para t-butyl benzoate 7

Allyl-4-t-butylbenzoate 7 (0.590 g, 2.7 mmol) in tetrahydro-furan (5 mL) was added to the titanium(II) species generated in situ at 0°C from titanium tetrachloride (1.02 g, 5.41 mmol, 0.59 mL), magnesium powder (0.324 g, 13.5 mg atom) and mercuric chloride (0.110 g, 0.4 mmol). Following similar reaction conditions and work up gave 4-t-butyl benzoic acid 10 (32%).

m.p.   : 163-164°C (lit.[15] m.p. 165-167°C)

The neutral portion on purification by flash chromatography (petroleum ether) yielded the hydrocarbon 18[15] (0.152 g, 19%).

m.p.   : 152-153°C (lit.[15] m.p. 154-155°C)

IR (KBr)   : 2920, 2850, 1445, 1260 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.3 (s, 18H), 2.9 (s, 4H), 7.3 (br s, 8H).

Ms (m/e)   : 294(M$^+$), 203, 161, 146, 91, 77.

Further elution with (5% ethyl acetate in petroleum ether) afforded allyl-4-t-butylphenyl ketone 9[18] (0.102 g, 19%).

IR (neat)   : 3100, 3000, 1690, 1650, 1620 cm^{-1}.

^{1}H NMR(CDCl$_3$) : 1.3 (s, 9H), 2.8 (t, 2H), 5.2 (d, 2H),

                     5.7 (m, 1H), 7.3 (s, 4H).

Ms (m/e)   : 202(M$^+$), 161, 91, 77.

Reductive cleavage of allyl-p-toluate 11

Allyl-p-toluate 11 (1.056 g, 6 mmol) in tetrahydrofuran (5 mL) was added to Ti(II) species generated in situ at 0°C from titanium tetrachloride (2.267 g, 12 mmol, 1.31 mL), magnesium powder (0.720 g, 30 mg atom) and mercuric chloride (0.240 g, 0.9 mmol). Following similar reaction conditions gave p-toluic acid

14 (0.4 g, 49%, m.p. 180-181°C) and the neutral portion. The neutral portion on purification by flash chromatography (petroleum ether) afforded the hydrocarbon 12 (0.221 g, 18%).

m.p.   : 79-81°C (lit.[24] m.p. 82°C)

IR (KBr)   : 3050, 3000, 2920, 1600 cm^{-1}

^{1}H NMR (CDCl$_3$) : 1.20 (s, 6H), 2.83 (s, 4H), 7.10 (s, 8H).

Further elution (5% ethyl acetate in petroleum ether) afforded allyl-p-tolyl ketone 13 (0.206 g, 22%).

IR (neat)   : 3100, 3040, 2950, 1650, 1610, 1585 cm^{-1}.

^{1}H NMR(CDCl$_3$)   : 1.21 (s, 3H), 2.82 (t, 2H), 5.21 (d, 2H),

                                5.34-5.96 (m, 1H), 7.37 (d, 3H), 7.45 (s, 1H).

Reductive cleavage of allyl-4-chlorobenzoate 15

Allyl-4-chlorobenzoate 15 (1.176 g, 6 mmol), in tetrahydrofuran (5 mL) was added to Ti(II) species generated *in situ* at 0°C from titanium tetrachloride (2.26 g, 12 mmol, 1.31 mL), magnesium powder (0.72 g, 30 mg atom) and mercuric chloride (0.24 g, 0.9 mmol). Following similar reaction conditions (2 h) gave the crude compound, which after removal of the 4-chlorobenzoic acid 18 (0.246 g, 26%) gave the neutral material.

m.p.   : 236-238°C (lit.[23] m.p. 243°C)

The neutral material on purification by flash chromatography over silica gel (petroleum ether) afforded the hydrocarbon 16 in 20% yield.

IR (neat)   : 3060, 3000, 2960, 1630, 1600 cm^{-1}

^{1}H NMR (CDCl$_3$) : 2.99 (s, 4H), 7.25 (br m, 8H).

Further elution (5% ethyl acetate in petroleum ether) afforded 4-chlorophenyl allyl ketone 17 (0.241 g, 22%).

IR (neat)   : 3010, 3000, 1690, 1620, 1600 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.68 (t, 2H), 5.28 (br s, 2H), 5.43-6.0 (m, 1H), 7.43 (m, 4H).

Reductive cleavage of allyl-3-chlorobenzoate 19

Allyl-3-chlorobenzoate 19 (0.392 g, 2 mmol), in tetrahydrofuran (5 mL) was added to Ti(II) species generated in situ at 0°C from titanium tetrachloride (0.756 g, 4 mmol, 0.44 mL), magnesium powder (0.243 g, 10 mg atom) and mercuric chloride (0.081 g, 0.3 mmol). Following similar reaction conditions (2 h) gave 3-chlorobenzoic acid 22 (0.08 g, 26%, m.p 154-156°C) and the neutral material. The neutral material on purification by flash chromatography over silica gel (petroleum ether) afforded the hydrocarbon 20 (0.087 g, 17%).

IR (CHCl$_3$)   : 3020, 2960, 1620, 1530 cm^{-1}

^{1}H NMR (CCl$_4$)   : 2.9 (s, 4H), 7.0-7.62 (m, 8H).

Further elution with 5% ethyl acetate in petroleum ether afforded the 3-chlorophenyl allyl ketone 21 (0.09 g, 25%).

IR (neat)   : 3080, 3000, 2920, 1680, 1645, 1600 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.65 (t, 2H), 5.0-5.2 (m, 2H), 5.3-5.9 (m, 1H) 7.15-7.60 (m, 4H).

Reductive cleavage of allyl cyclohexylcarboxylate 23

    Allyl cyclohexylcarboxylate 23 (0.672 g, 4 mmol), in tetra-hydrofuran (5 mL) was added to Ti(II) species generated in situ at 0°C from titanium tetrachloride (1.51 g, 8 mmol, 0.88 mL), magnesium powder (0.48 g, 20 mg atom) and mercuric chloride (0.162 g, 0.6 mmol). Following similar reaction conditions (2 h) gave the crude compound, which after the removal of cyclohexyl-carboxylic acid 26 (0.102 g, 21%) gave the neutral material. The neutral material on purification by flash chromatography over silica gel and first eluting with (petroleum ether) afforded 24 (0.080 g, 17%).

IR (neat)   : 2920, 2860, 1450, 1260 cm^{-1}

^{1}H NMR (CCl$_4$) : 0.96-1.48 (br, 20H), 1.74 (br s, 2H) 5.18
                      (dd, 2H).

Ms (m/e)   : 192(M^{+}).

Further elution (5% ethyl acetate in petroleum ether) yielded allyl cyclohexyl ketone 25[22] (0.086 g, 15%).

IR (neat)   : 2920, 2860, 1700, 1450 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.2-1.9 (m, 10H), 2.3 (d, 2H), 5.2 (d, 2H),
                      5.7-6.1 (m, 1H).

Ms (m/e)   : 152(M^{+}), 111, 83.

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C H A P T E R - II

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF TRICYCLOPENTANOIDS

II.1 INTRODUCTION

The interest on the natural products of polyquinanes started only over a decade and half. Ever since their isolation and structural elucidation, there has been considerable interest among the fraternity of organic chemists to the challenge posed by this polyquinane family, especially from triquinanes owing to the topology of their ring fusion.

These triquinanes isolated mostly from plant, marine and fungal sources have interesting structural features and biological applications. Until now there are over eighty triquinanes that have been identified from the natural sources and have been classified as either linear, non-linear (angular) or propellane depending on the topology of their ring fusion.[1] The biologically most important terpenes are found in hirsutane (linear) and pentalenane (angular) families of compounds. Their significant biological activities range from antibiotic action to antitumor properties.[2] Not surprisingly, the above factors coupled with novelty and the complexity of their structures have spawned intense synthetic activity.

Among the polyquinanes the two stereoisomeric C_{11}-triquinanes (cis, syn, cis 1 and cis, anti, cis 2) representing three linearly fused cyclopentane rings, have received relatively

greater attention due to the fact that the cis, anti, cis isomer 2 embraces the basic carbocyclic framework of biologically important sesquiterpenoids of hirsutane family e.g. coriolin 4 and capnellene 5 (Fig. II. A. 1.).

A number of synthetic approaches have been successfully completed and are well documented in literature.[1] Among these synthetic approaches a few are very impressive.

Mehta and coworkers[3] have constructed the tricyclic ring with readily available starting materials. The beauty of this approach derives from the stepwise (photo/thermal) metathesis of Diels-Alder adducts derived from cyclopenta-1,3-diene and 2,5-disubstituted p-benzoquinone. This methodology has been applied for the synthesis of sesquiterpene hydrocarbon (±)-Hirsutene 3, (±)-Coriolin 4 and (±)-Capnellene 5. Thus cyclopentadiene and 2,5-dimethyl-p-benzoquinone furnished a [4+2] adduct having 13 carbons out of 15 carbon atoms of hirsutene 3. A series of regio- and chemoselective operations on this adduct yielded the desired compound 3 in about 10 steps (Scheme II. A. 1).

The key step in the cyclopentane ring annulation strategy of Greene et al[4] involves the successive ketene addition and ring expansion strategy (Scheme II. A. 2)

The methodology adopted by Curran and coworkers[5] involves a tandem radical induced olefin cyclization to the construction of 3 (Scheme II. A. 3).

FIGURE II. A.1
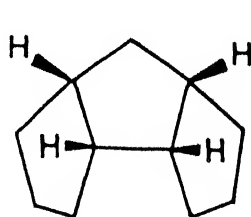
1
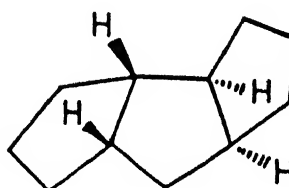
2
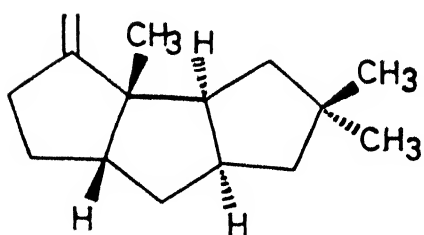
HIRSUTENE **3**
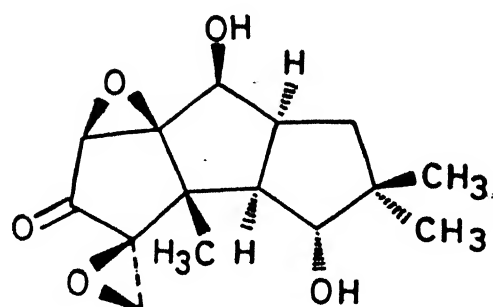
CORIOLIN **4**
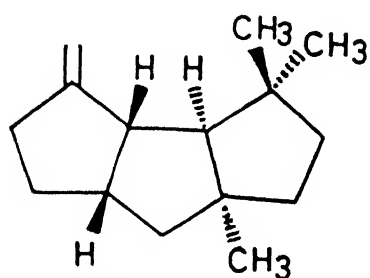
CAPNELLENE **5**

SCHEME II.A.1[3]

$\Phi H, \Delta$

$h\nu$, EtoAc

500°C

3

(±) - HIRSUTENE

SCHEME II.A.2[4]

1. CH_3—C—Cl—$\bullet$=O

2. CH_2N_2

1. $NaBH_4$

2. $Cr(ClO_4)_2$

3

SCHEME II.A.3[5]

$$\xrightarrow{\text{Bu}_3\text{Sn}^\bullet}$$

$$\xrightarrow{\text{Bu}_3\text{SnH}}$$ **3**

SCHEME II.A.4[6]

$$\xrightarrow{\text{ISiMe}_3}$$

$$\longrightarrow \longrightarrow \quad \underline{3}$$
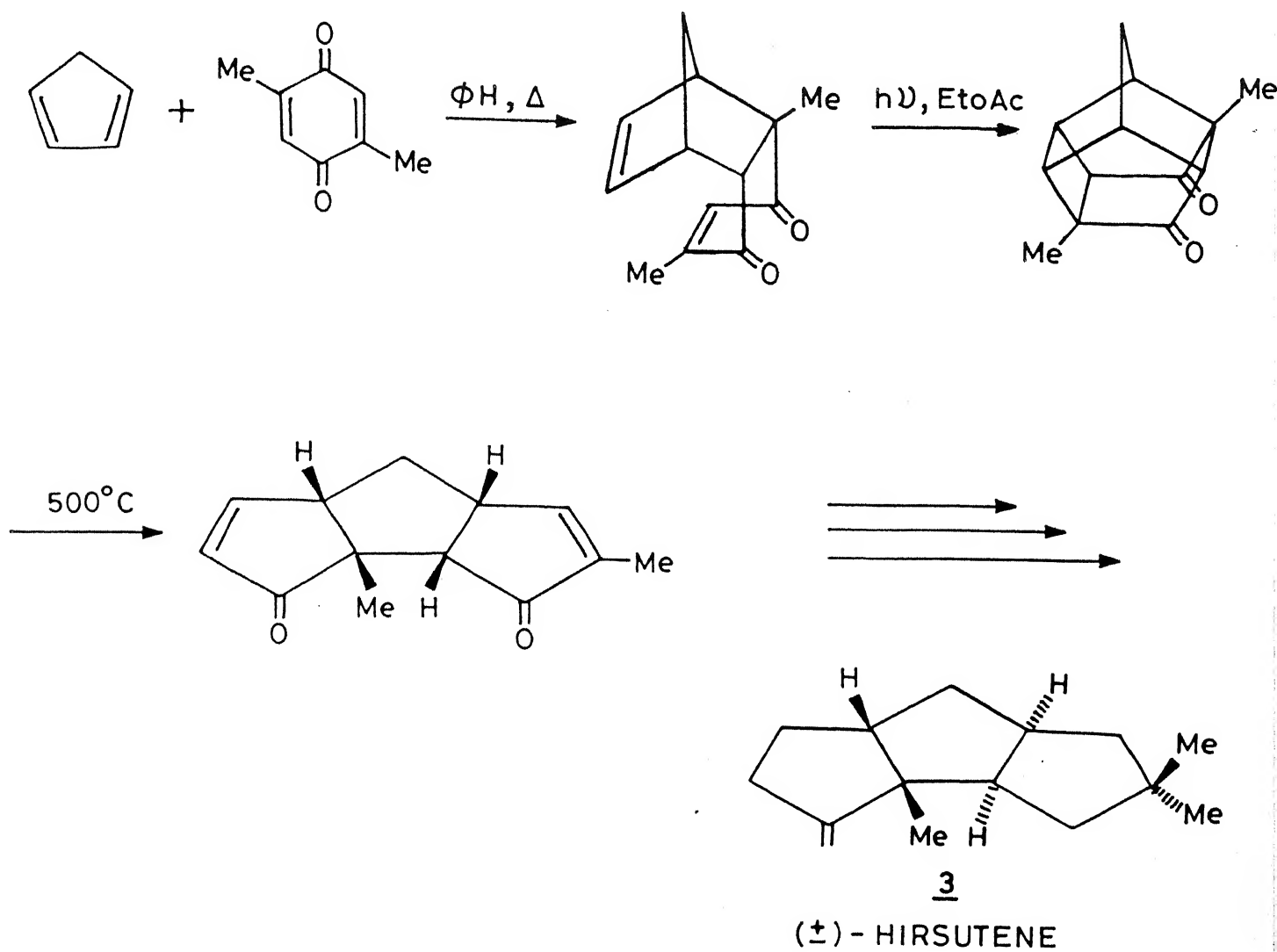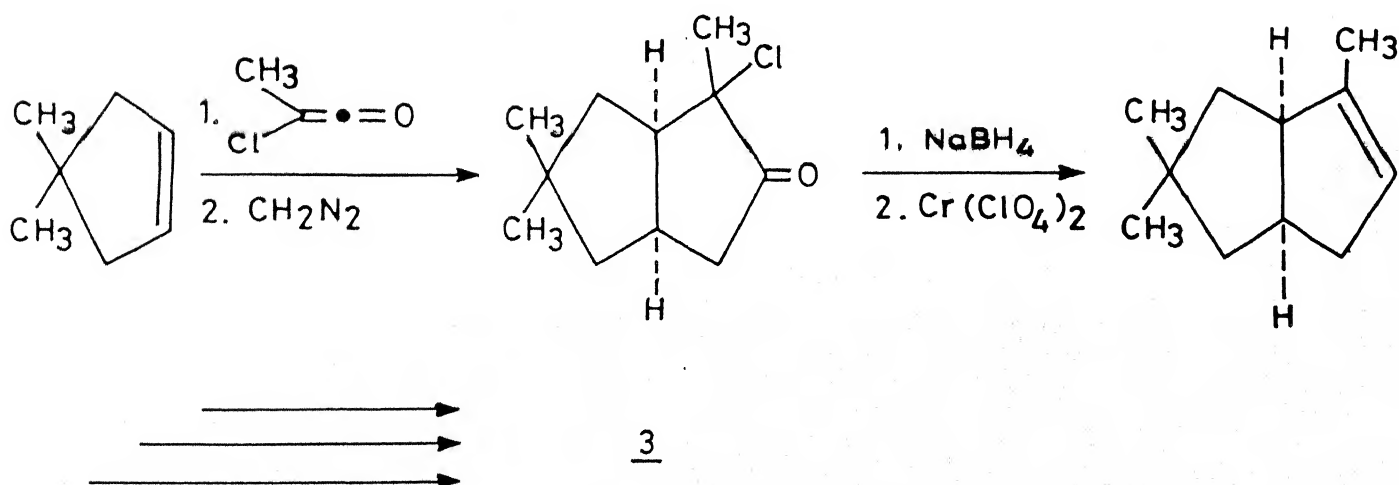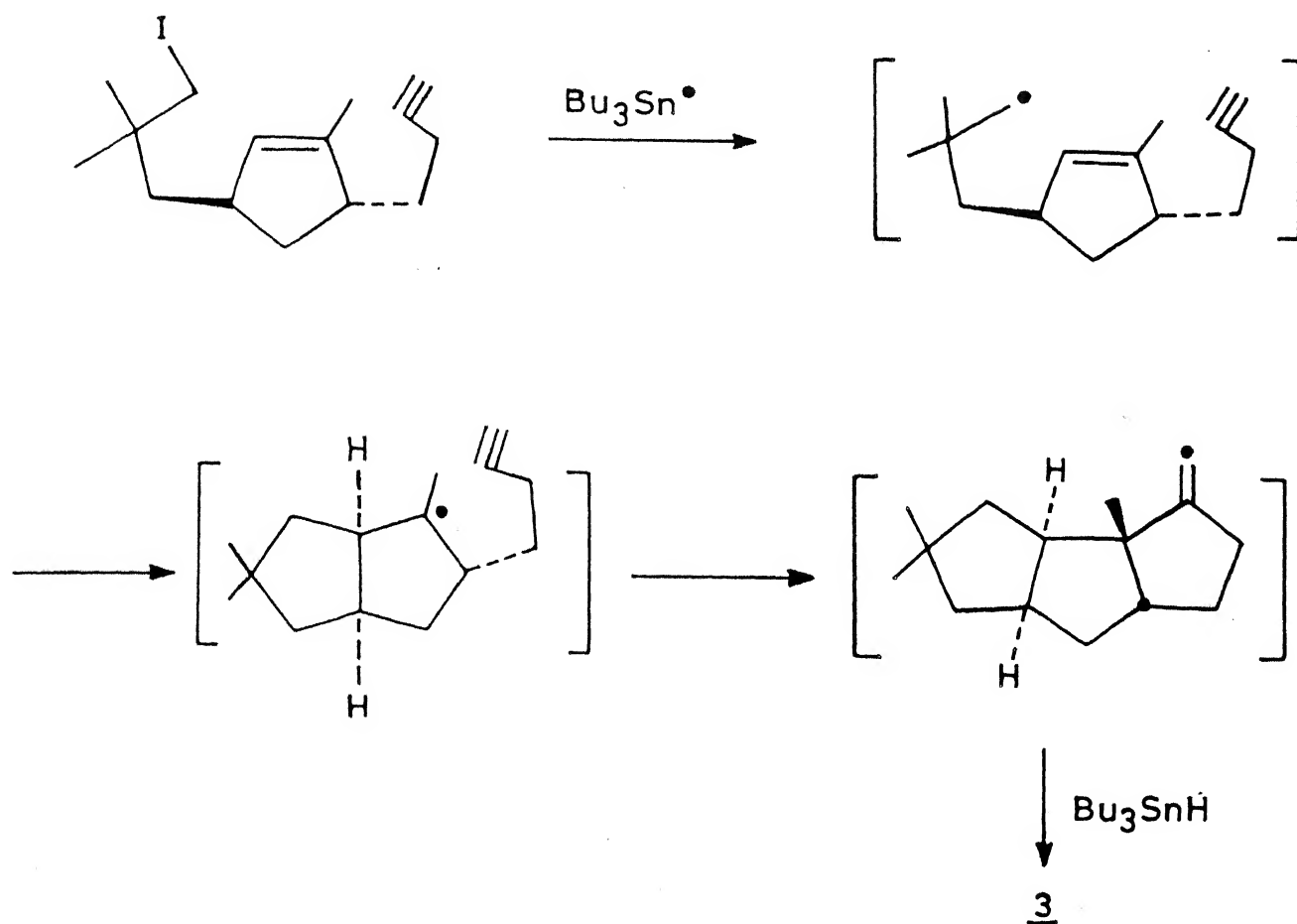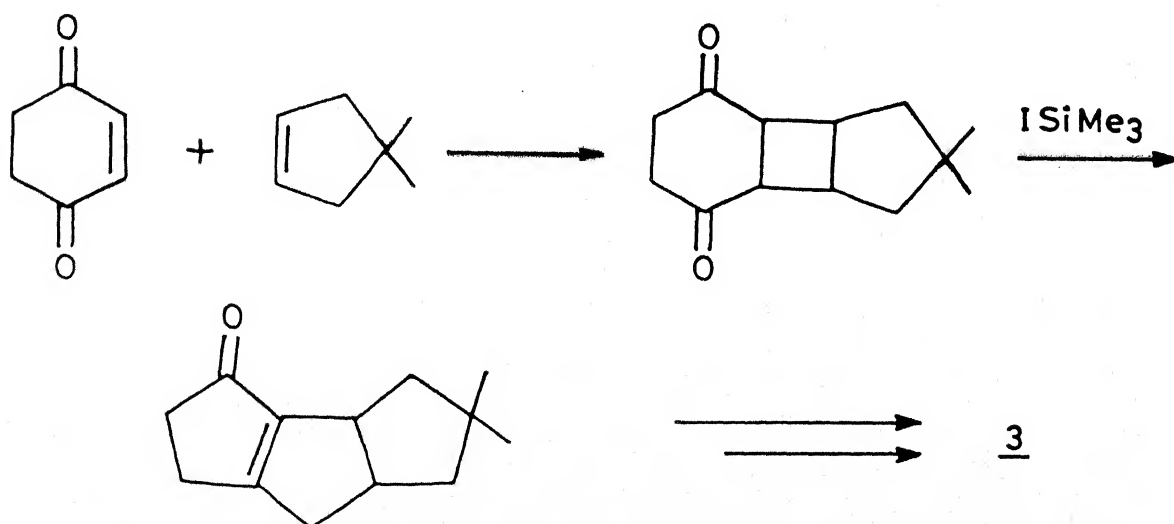
Herein a radical is generated which suffers two successive hex-5-enyl like radical cyclizations and final hydrogen abstraction to give 3.

Ioyoda et al[6] have used the tricyclic 2,5-diketone ring system for the novel construction of $[6.3.0.0^{2,6}]$ undecane skeleton with iodotrimethylsilane (Scheme II. A. 4).

Our effort on the synthetic approaches to these challenging linearly fused triquinanes are essentially by two approaches.
1. Intermolecular cycloaddition approach.
2. Intramolecular vinylketene-olefin cycloaddition approach.

A number of synthetic methodologies adopted for the synthesis of triquinane natural products so far, were by intermolecular cycloaddition approach. A few important approaches in this direction have already been discussed above. Intramolecular vinyl ketene-olefin cycloaddition approach is being increasingly used as a general methodology for the construction of complex natural products, hence, some recent developments in this area are illustrated so that the present work can be put in the right perspective.

II.1.a Intramolecular ketene-olefin cycloaddition methodology

The stereospecific [2+2] cycloaddition of ketenes to alkenes has become a valuable method for the synthesis of cyclobutanones and compounds derived from them.[7] Although isolated

examples of intramolecular [2+2] cycloaddition of ketenes to alkenes are known,[8,9] it is only recently systematic studies to develop this as a general synthetic methodology have been taken up.[10,11] Pioneering work of Snider and coworkers have shown some interesting features of this intramolecular cycloaddition reaction.[12] This reaction promises to extend the scope of the cycloaddition to less reactive alkenes and ketenes and to provide an efficient route to complex polycyclic compounds. The intramolecular nature of the reaction has led to a high degree of stereo- and regioselectivity. Snider has shown that the electronic effects of substituent on the double bond rather than connectivity pattern, control the regiochemistry of cycloaddition (Scheme II. A. 5).[11]

Thus alkenes 6 and 8 in which the internal carbon is more substituted react to give bicyclo [3.2.0] heptanes 7 and 9 respectively. Alkene 10 in which the terminal carbon is more substituted reacts to give bicyclo [3.1.1]heptane 11. A complementary study involving intramolecular cycloaddition of keteniminium salts to olefins has been reported by Ghosez.[10]

Snider[13] has also reported a facile intramolecular cycloaddition of alkenes with vinyl ketenes prepared by regiospecific deprotonation of β,β-disubstituted, α,β-unsaturated acid chlorides (Scheme II. A. 6).

In general the cycloadducts with an exocyclic double bond are obtained from vinyl ketenes derived from deprotonation of the methyl group syn to the acid chloride rather than a methylene

SCHEME II.A.5[11]

6 → Et₃N → 7

8 → "" → 9

10 → "" → 11
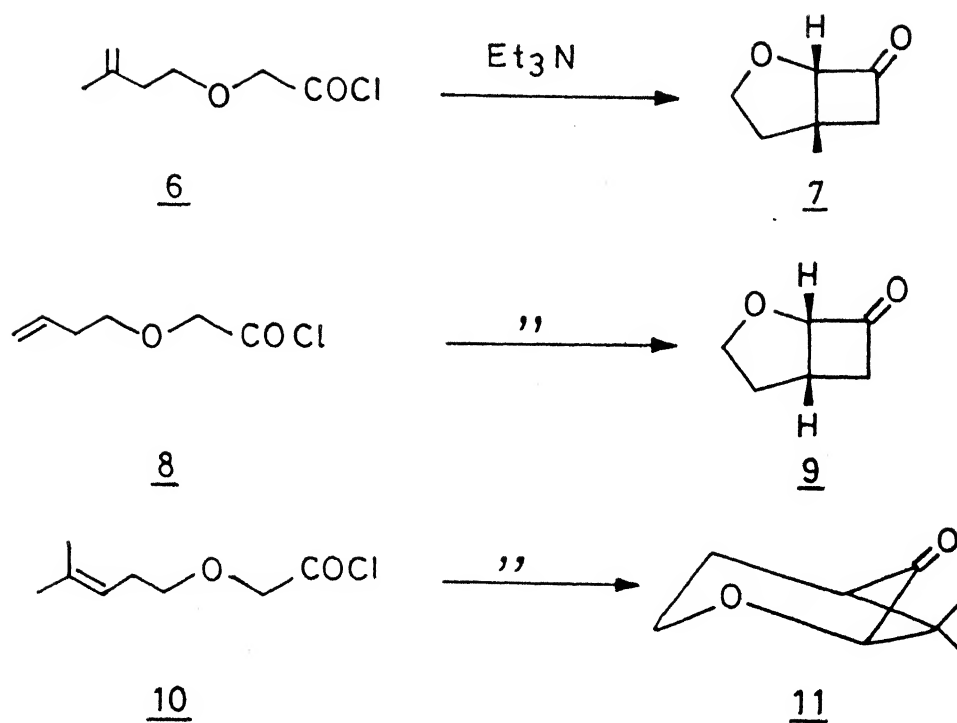
SCHEME II.A.6[13]
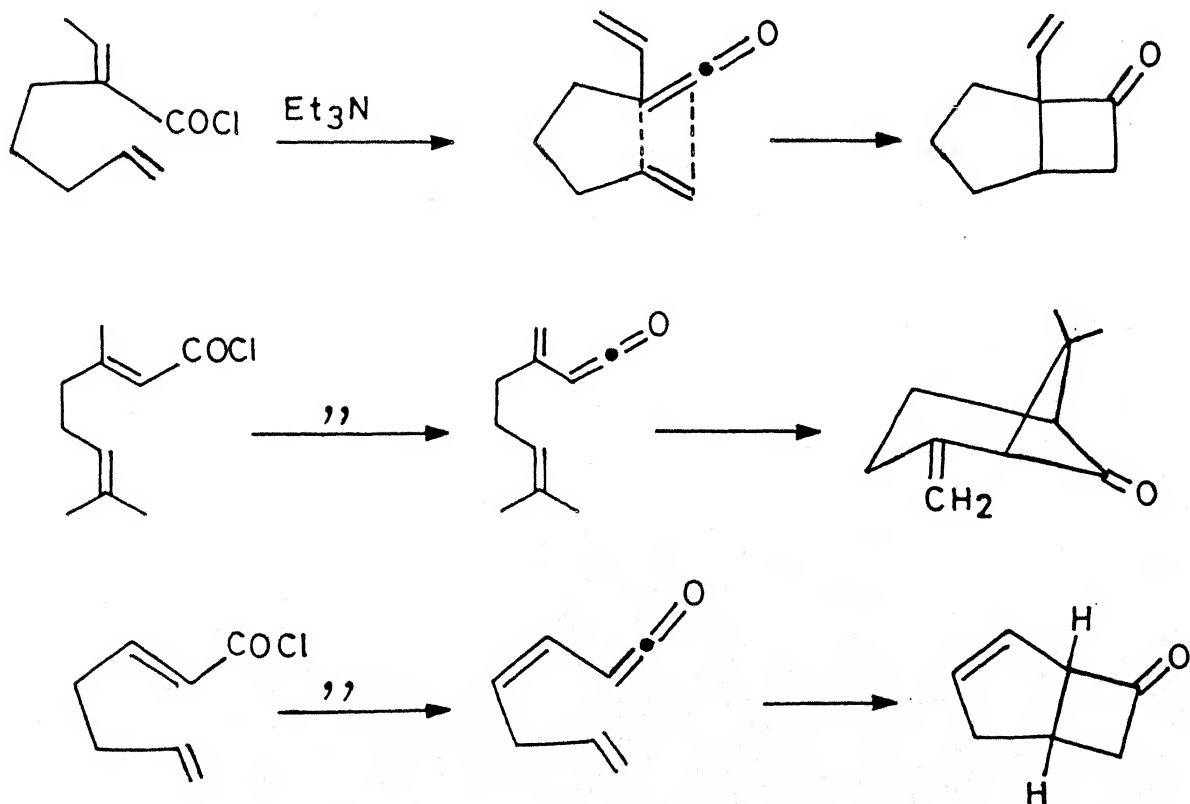
anti to the acid chloride. This methodology was utilised in the synthesis of β-pinene, β-cis-bergomotene, β-copaene etc.[14] These workers have been able to establish that the position of deprotonation of β,β-disubstituted α,β-unsaturated acid chlorides with amine bases is controlled by kinetic acidity of the substituents.

Ernst and coworkers have recently reported the intramolecular vinyl ketene-olefin cycloaddition approach to the construction of linearly annelated[15] and angular annelated triquinane derivatives[16] (Scheme II. A. 7 and II. A. 8).

II.2 Results and Discussion

The objective of the present study was to construct the basic linearly fused tricyclic undecane carbon skeleton with cis, anti, cis geometry as it exists in the naturally obtained material through economically viable routes and in fewer number of steps. This would serve as a model for the synthesis of tricyclopentanoid natural products like hirsutene 3, coriolin 4 after functional group modifications.

Our effort in this direction has been multipronged. One of the approaches successfully executed from our laboratory involved the iterative oxidative cyclization and rearrangement strategy[17] (Scheme II. A. 9). The reaction sequence involves the formation of spirolactone 13 by substituent directed oxidation of hydroxy

SCHEME II.A.7[15]

SCHEME II.A.8[16]

R = Cl
= OMe
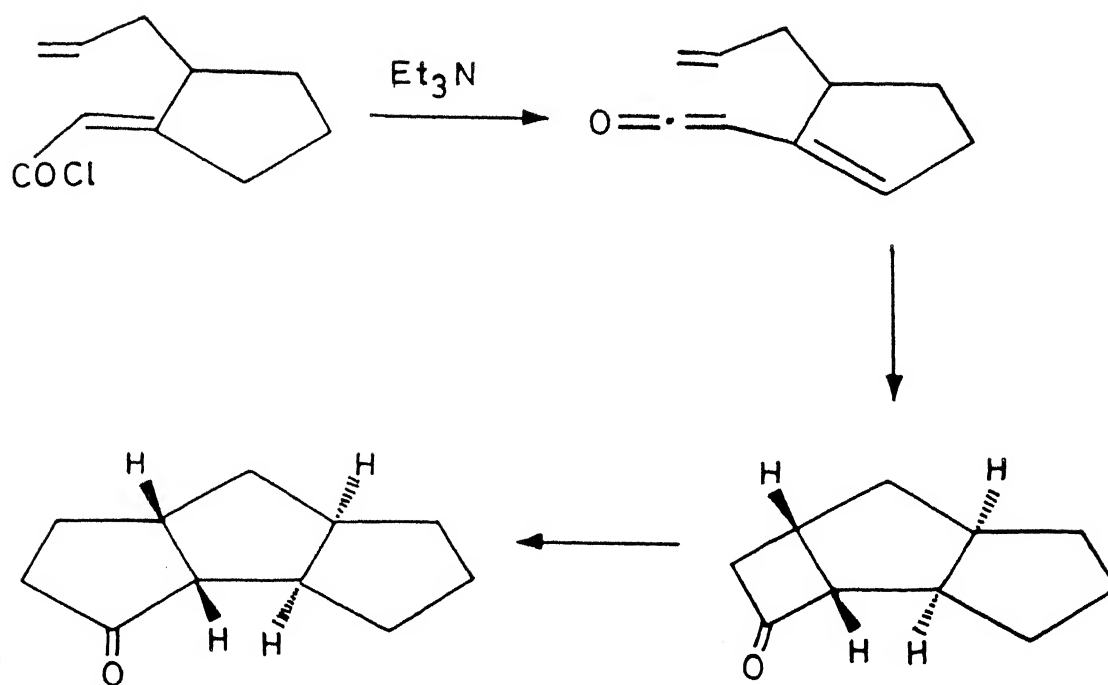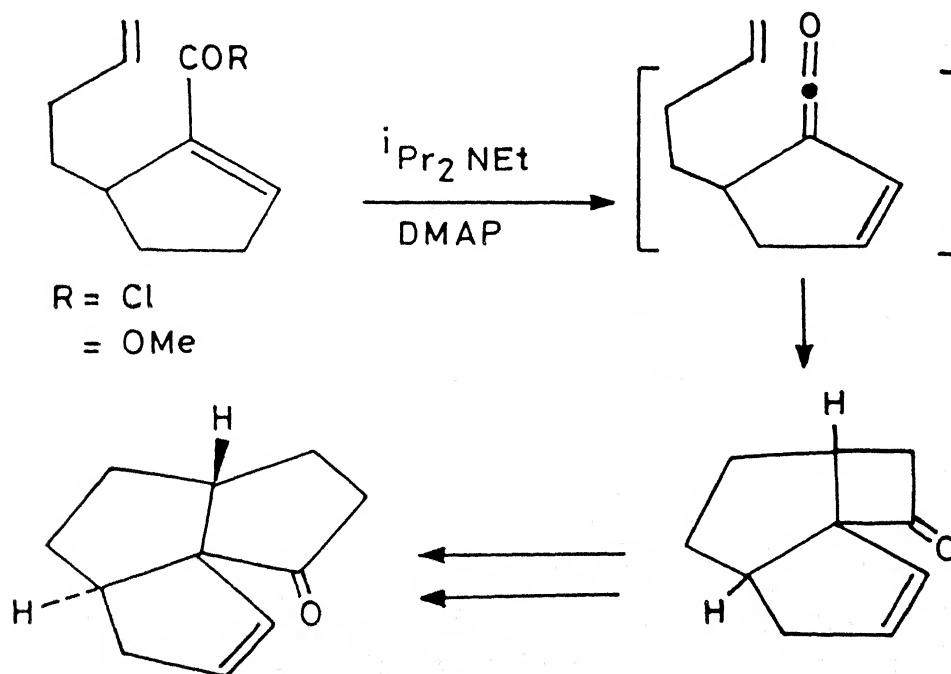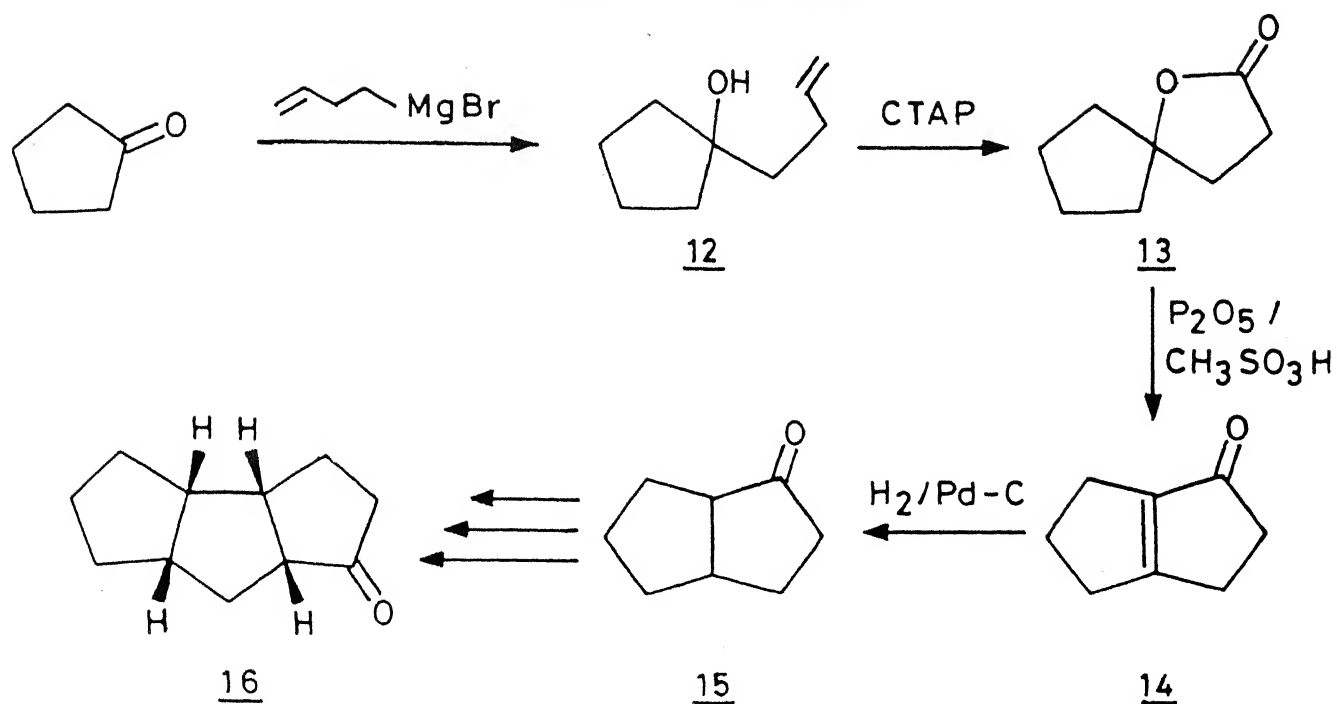
SCHEME II.A.9[17]

SCHEME II.A.10
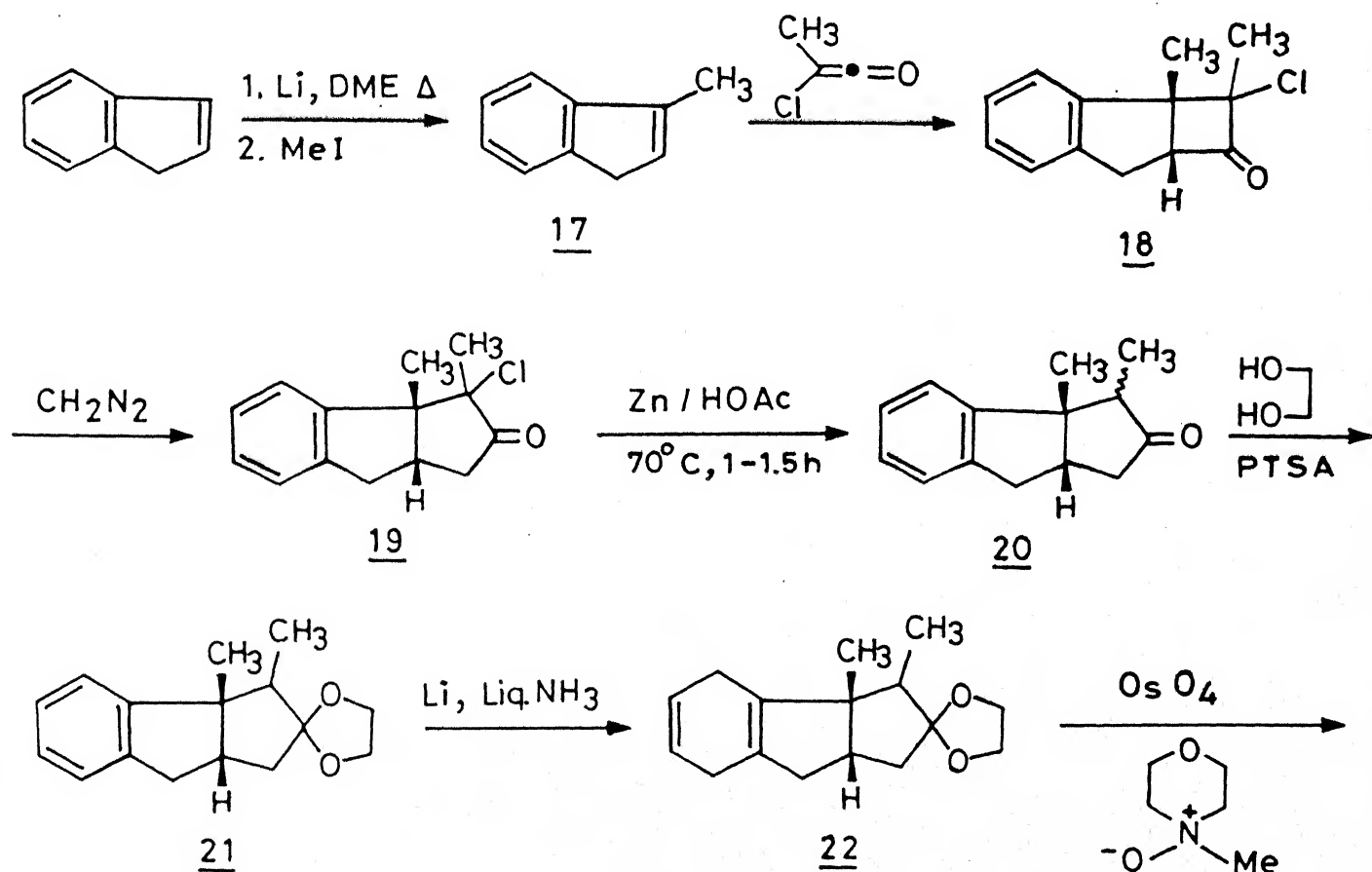
Contd.———
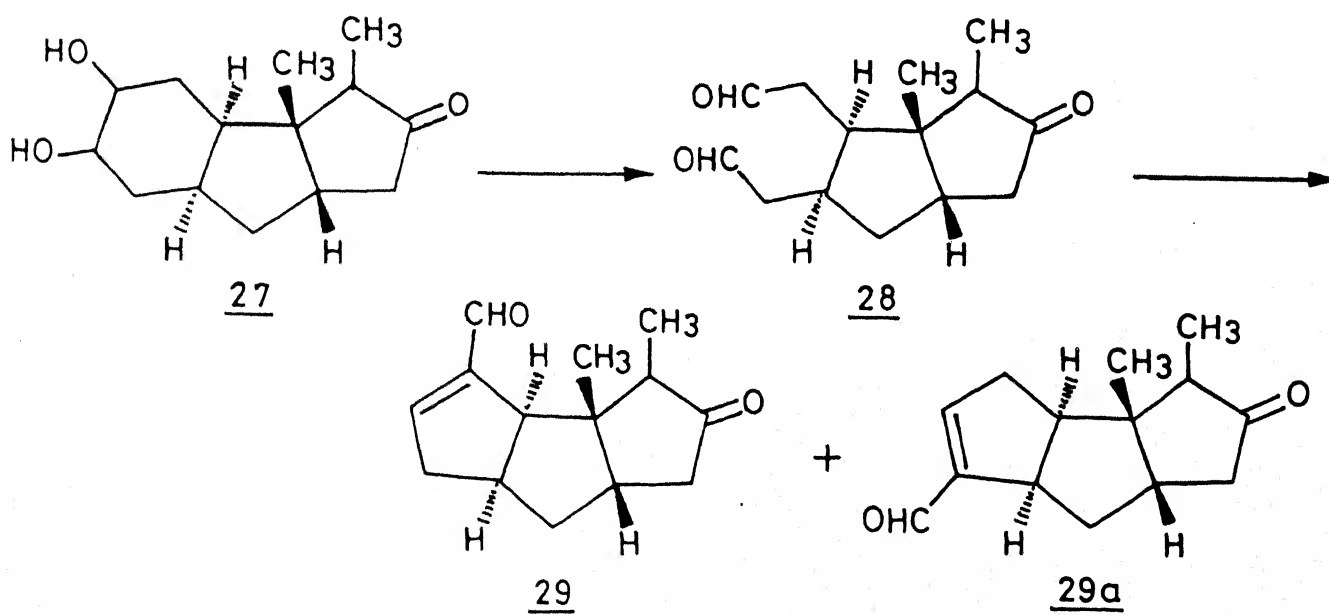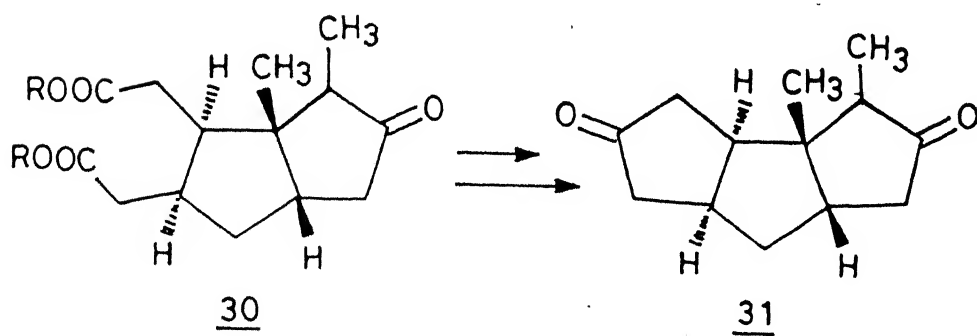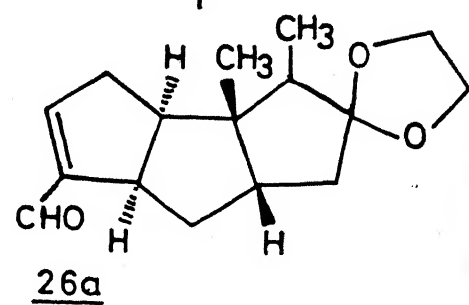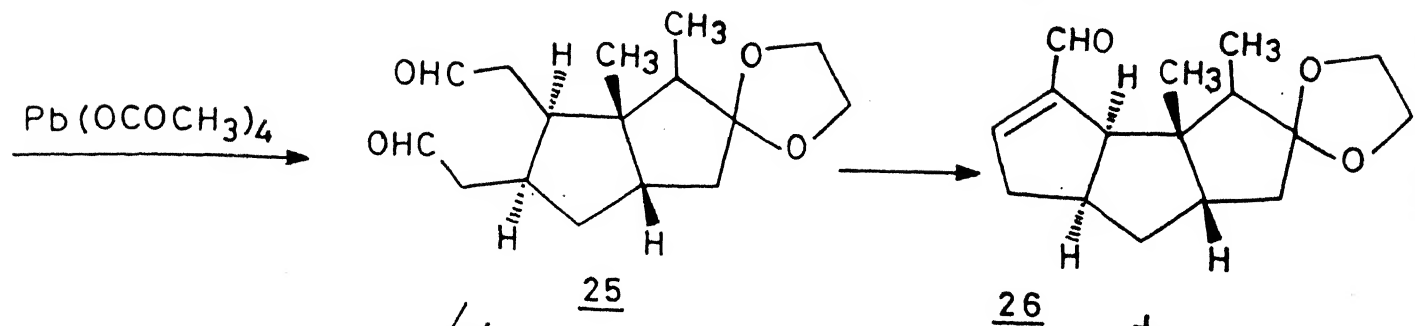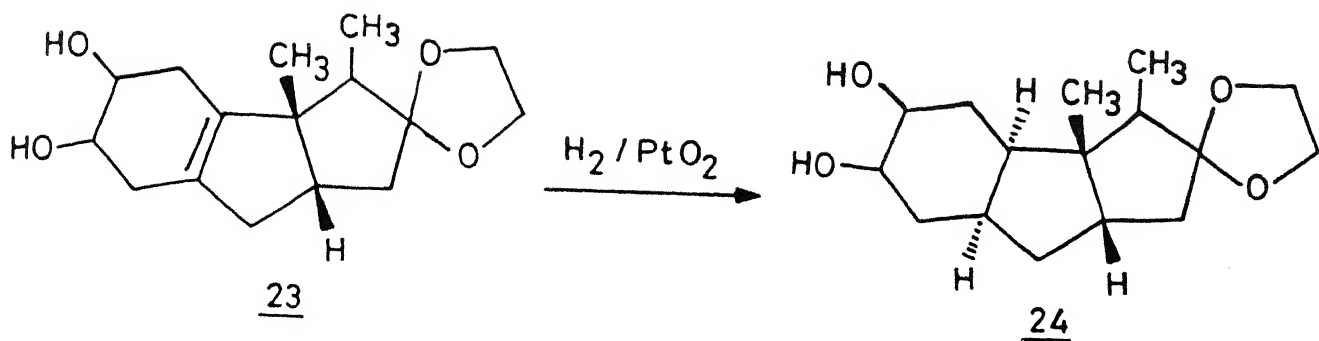
olefin 12, which rearranges with methane sulfonic acid/phosphorous pentoxide to give the bicyclic α,β-unsaturated ketone 14. Reduction of the double bond gives the bicyclic ketone 15 and repetition of the above sequence affords the cis-syn-cis tricyclic undecane skeleton 16.

II.2.a Intermolecular cycloaddition approach (Methylindene route)

Indene was alkylated with methyl iodide to give a mixture of 1- and 3-methylindene[18]. The crude product was isomerized by treatment with triethylamine and fractionated to get 3-methyl indene in more than 90% purity[19]. Other methods of preparation of 17 gave inferior yields[20,21].

3-Methylindene 17 was treated with methylchloroketene generated in situ from freshly distilled 2-chloropropionyl chloride[22] and triethylamine. After 2 h reflux in petroleum ether (40-60°C) and chromatographic purification gave the adduct 18 (72%). One carbon homologation of 18 was done with freshly generated diazomethane to afford the cyclopentanone 19.[23] Dehalogenation of 19 with zinc/acetic acid at 70°C for 1-1.5 h afforded 20 (97.5%)[23]. Compound 20 was protected as its ethylene ketal 21. Lithium ammonia reduction of ketal 21 in the presence of ethanol as a proton source resulted in the formation of 22 in excellent yield (98.8%). The diol 23 was obtained (78%) from 22 by catalytic osmylation reaction[24].
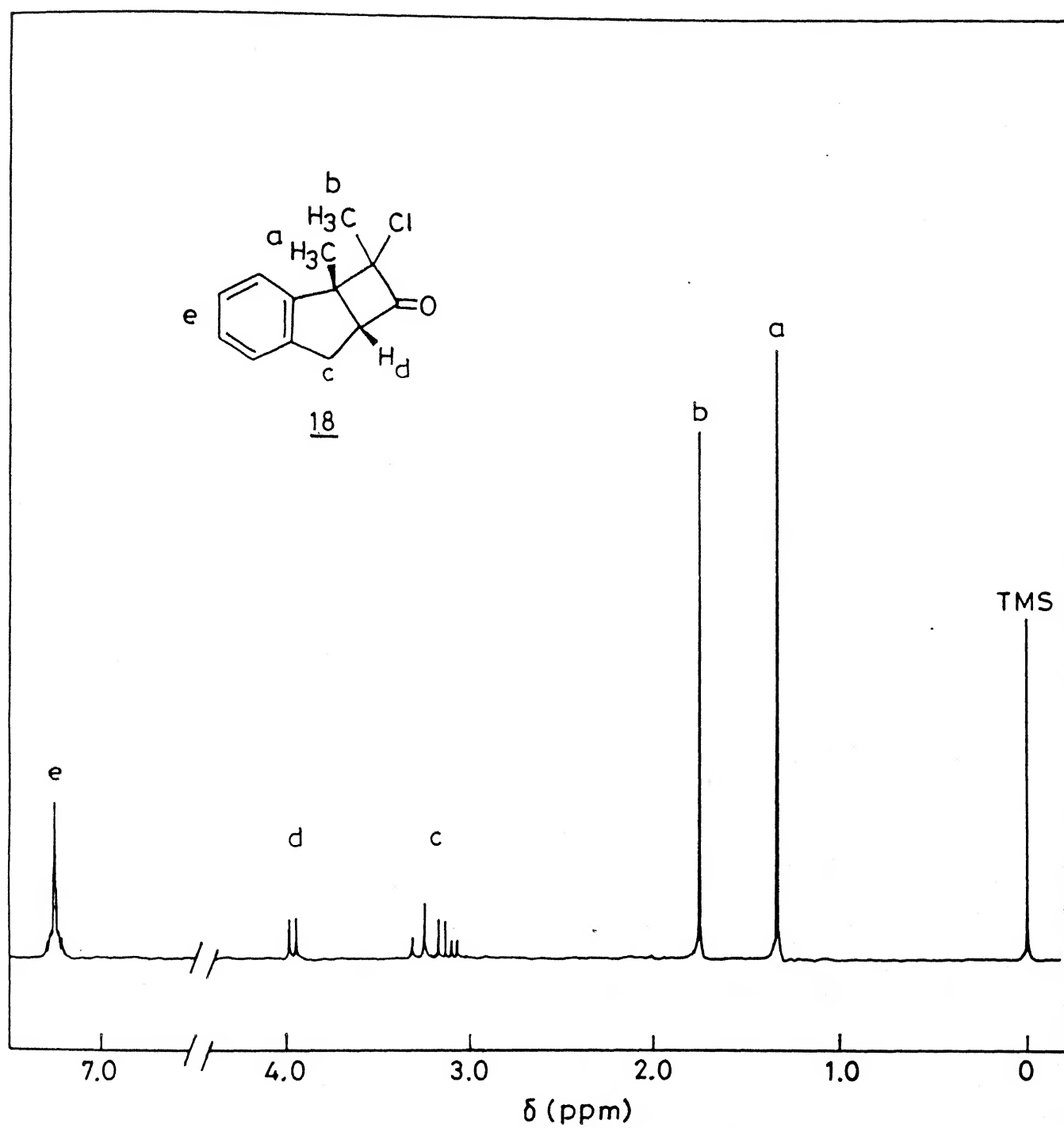
^{1}H NMR spectrum (250 MHz) of <u>18</u>.
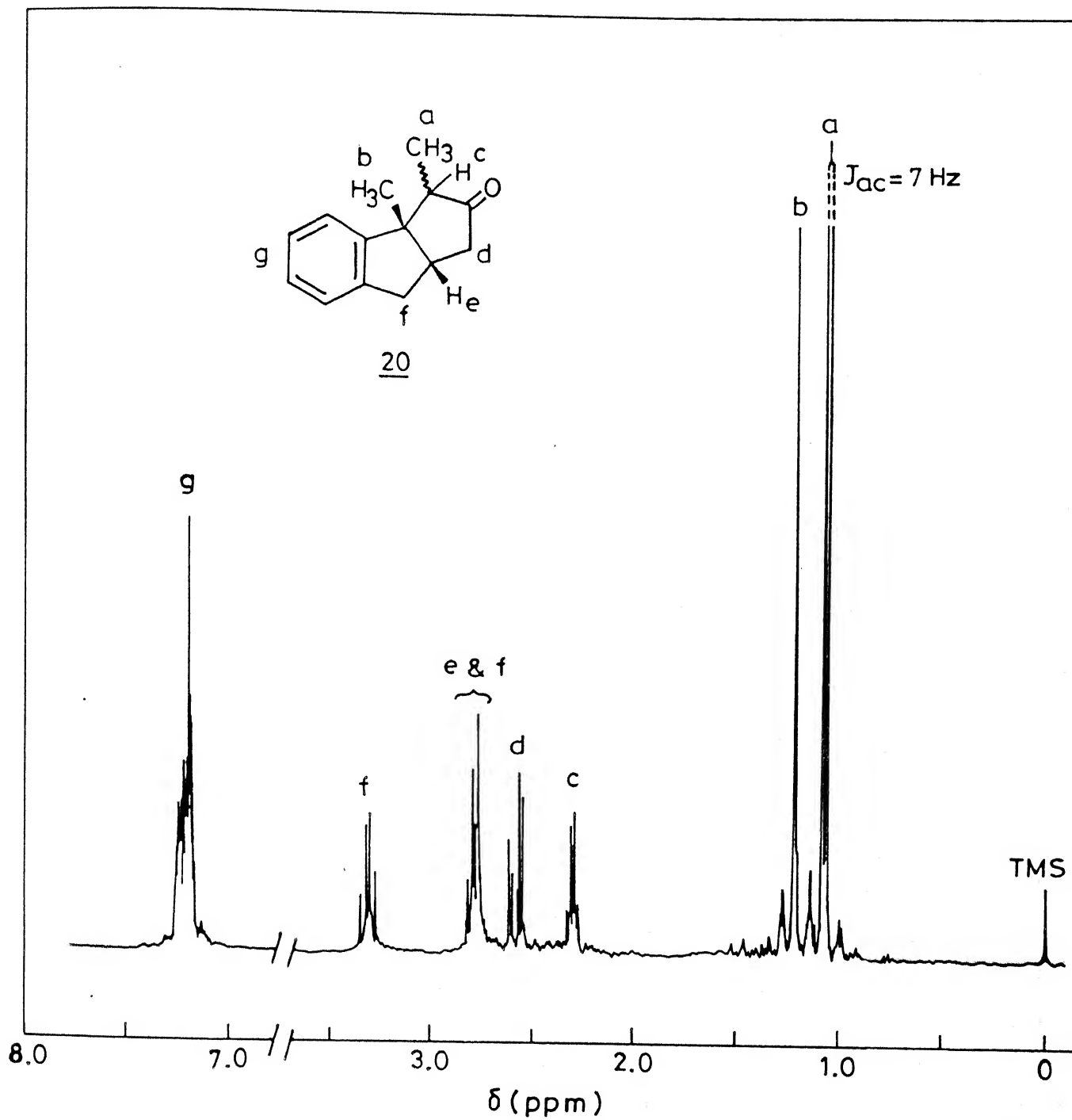
^{1}H NMR spectrum (400 MHz) of 20.
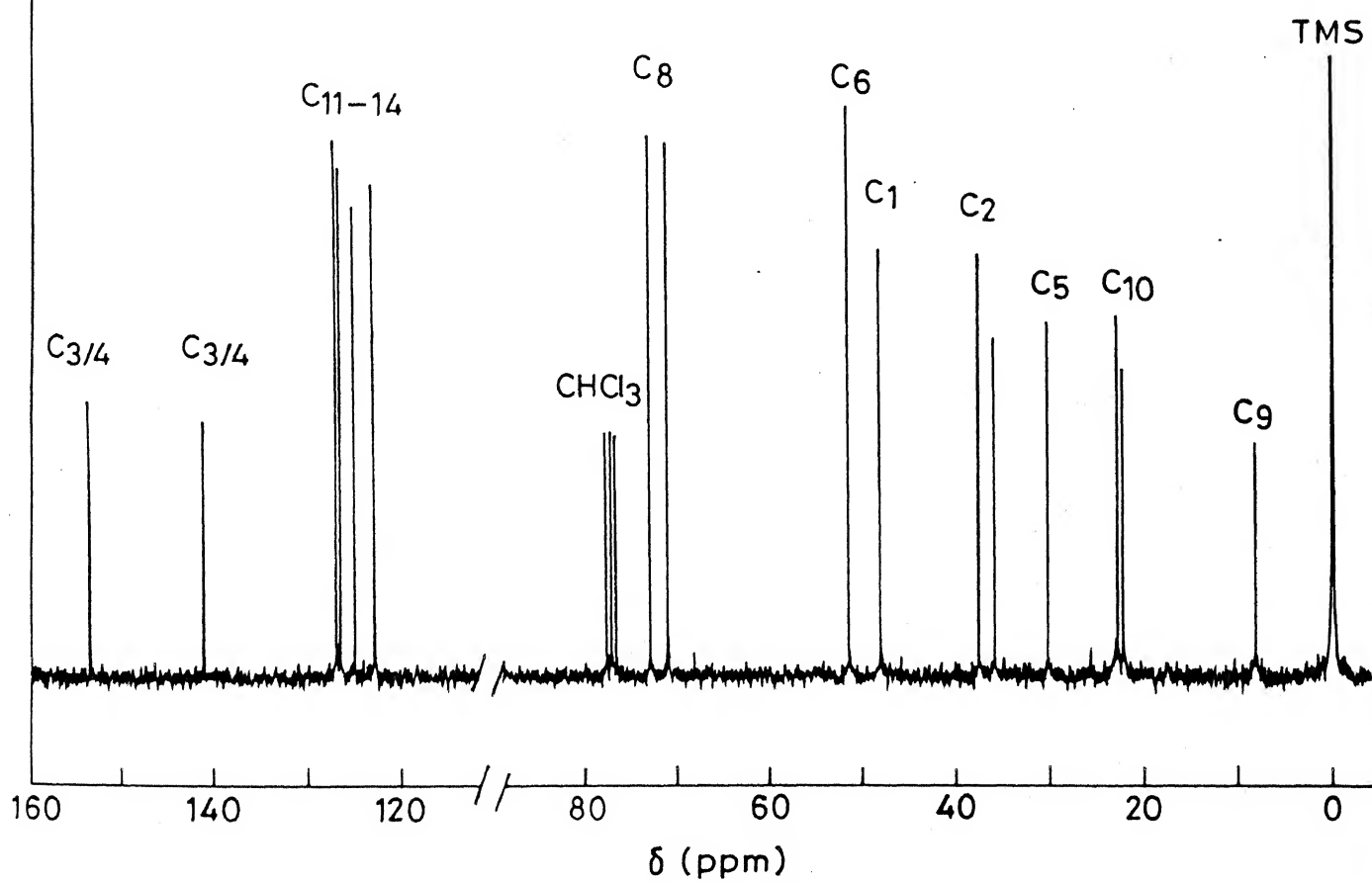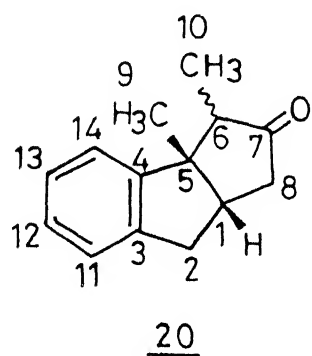
^{13}C NMR spectrum (62.9 MHz) of 20.
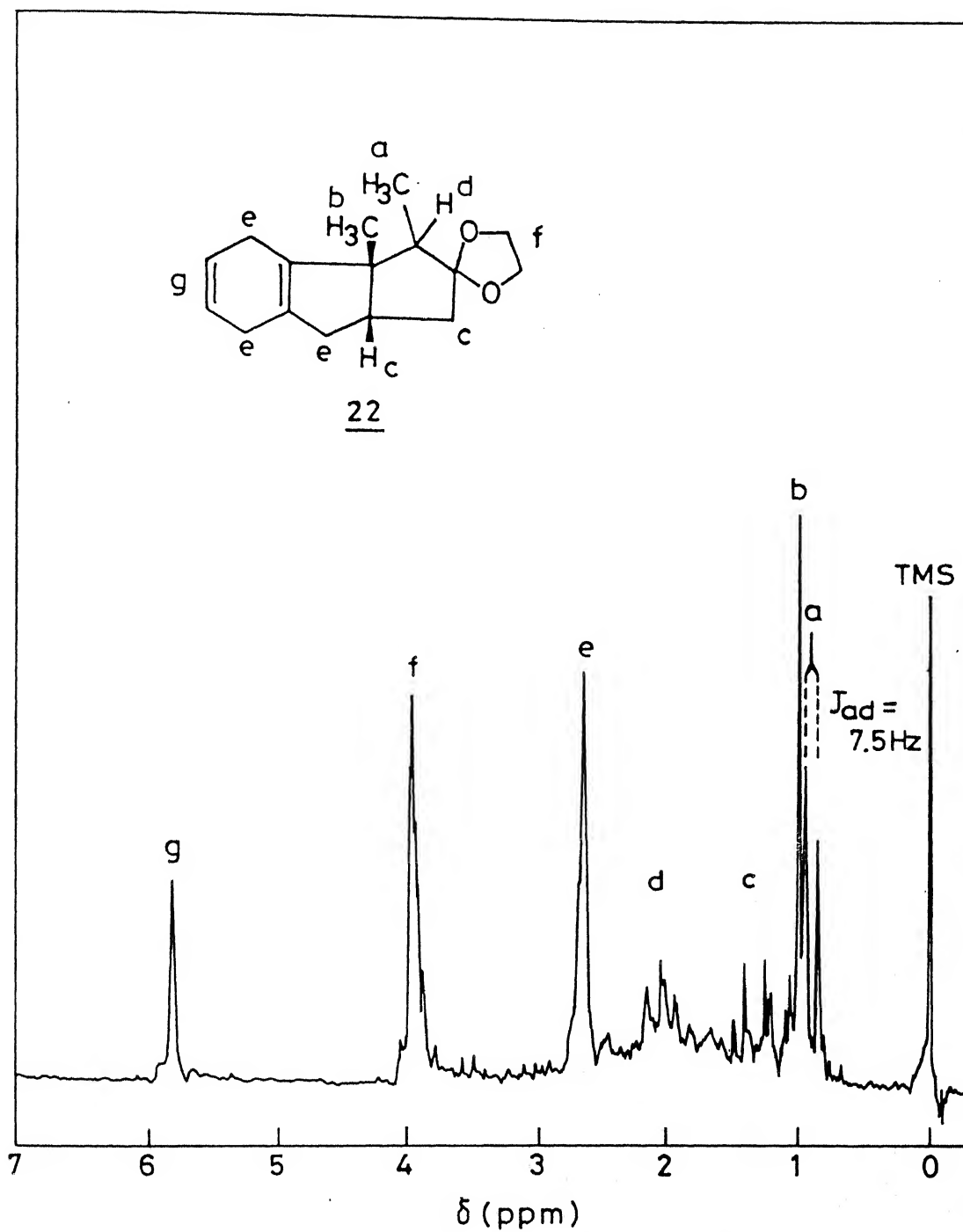
^{1}H NMR spectrum (80 MHz) of 22.
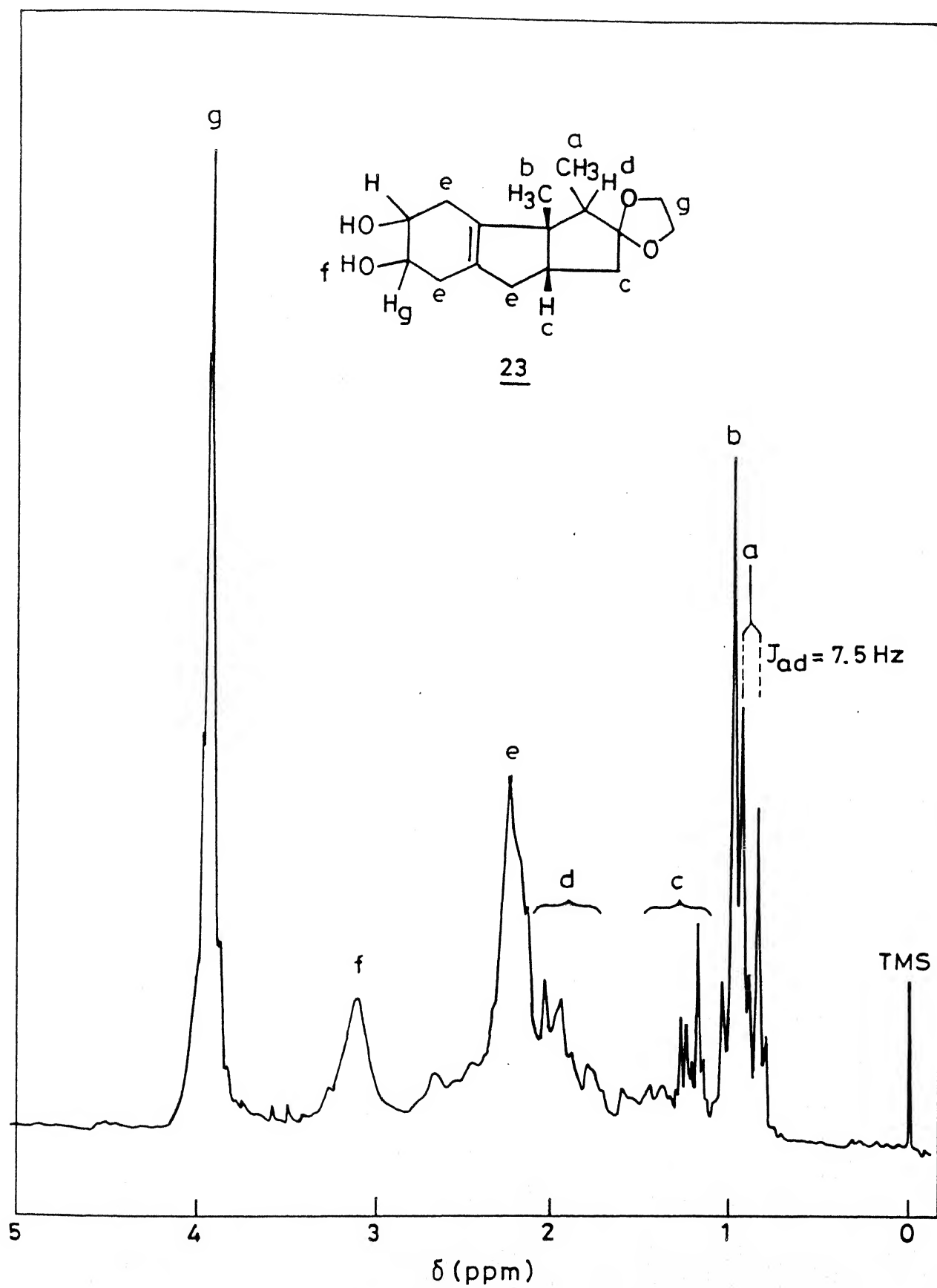
^{1}H NMR spectrum (80 MHz) of 23 .

Various catalysts (Pd/C, Pt/C, PtO_2) in variety of solvents (ethanol, ethyl acetate, acetic acid) were tried to reduce the tetrasubstituted double bond in 23. After considerable effort, it was found that activated Adam's catalyst (PtO_2) in methanol at a hydrogen pressure of 50-60 psi was reasonably successful to afford the cis-anti-cis tricyclic compound 24. Our initial strategy was to oxidatively cleave the diol 24 to the dialdehyde 25 and effect an aldol cyclization to give the unsaturated aldehyde 26 and 26a. Accordingly treatment of diol 24 with lead tetraaceate in benzene at 25°C resulted in the formation of the dial 25 in high yield (91%). Although there is a lot of precedence in the literature for this type of aldol cyclization,[25] dialdehyde 25 under a variety of conditions and different reagents invariably yielded none of the desired product 26 and 26a. Typical reagents which proved ineffective for aldol reaction in the present case were piperidinium acetate[25], sodium metaperiodate - potassium hydroxide[26] and dibenzylammonium trifluoroacetate[27]. The aldol reaction was also tried on the dialdehyde 27 without the ketal protecting group and was found to be unsuccessful. The reason for the failure of this reaction remains unclear (Scheme II.A.10). Because of the difficulties encountered in dealing with the dialdehyde 25 this route was not pursued further for the time being. It would be possible to construct the cis-anti-sys tricyclopentane skeleton 31 from 25 by conversion to the diester 30 followed by a Dieckmann's cyclization.

II.2.b Intermolecular [4+2] cycloaddition approach

(cyclopentadiene - maleic anhydride route)

In the second approach the synthetic pathway adopted has been delineated in Scheme II. A. 11. Herein we have utilised the endo adduct 32 formed in very good yield (96%) from Diels-Alder reaction of cyclopentadiene and maleic anhydride for the construction of tricyclic skeleton. The adduct 32 on treatment with the Grignard reagent derived from 1,4-dibromobutane afforded after acid hydrolysis with 10% hydrochloric acid the spirolactone 33[28] in 65% yield. Our initial attempts to functionalise the olefin 33 by Wacker's process[29] using palladium chloride, cuprous chloride proved futile. Surprisingly the attempted hydroboration with BH_3/THF followed by oxidative work-up failed to give any of the desired alcohol 34 and 34a. The starting material was recovered unchanged. In our laboratory it has recently been shown that olefins on treatment with benzyltriethylammonium borohydride and chlorotrimethylsilane in dichloromethane followed by aqueous work-up yielded the corresponding alcohols in good yield.[30] The mechanistic details of this novel reaction are being worked out in our laboratory. We decided to try out this methodology in the case of olefin 33. Accordingly olefin 33 was treated with one equivalent of benzyl triethylammonium borohydride and chlorotrimethylsilane in dichloromethane at 0°C for 1-2 h afforded two regio isomeric alcohols 34 and 34a in 67.5% yield. This mixture of alcohols was oxidized by pyridinium chlorochromate[31] to give a mixture of keto lactones 35 and 35a in 3:2 ratio (64%) yield. At

SCHEME II.A.11

32

33   **34 & 34a**

35   **36**

37   **38**

35a   **36a**
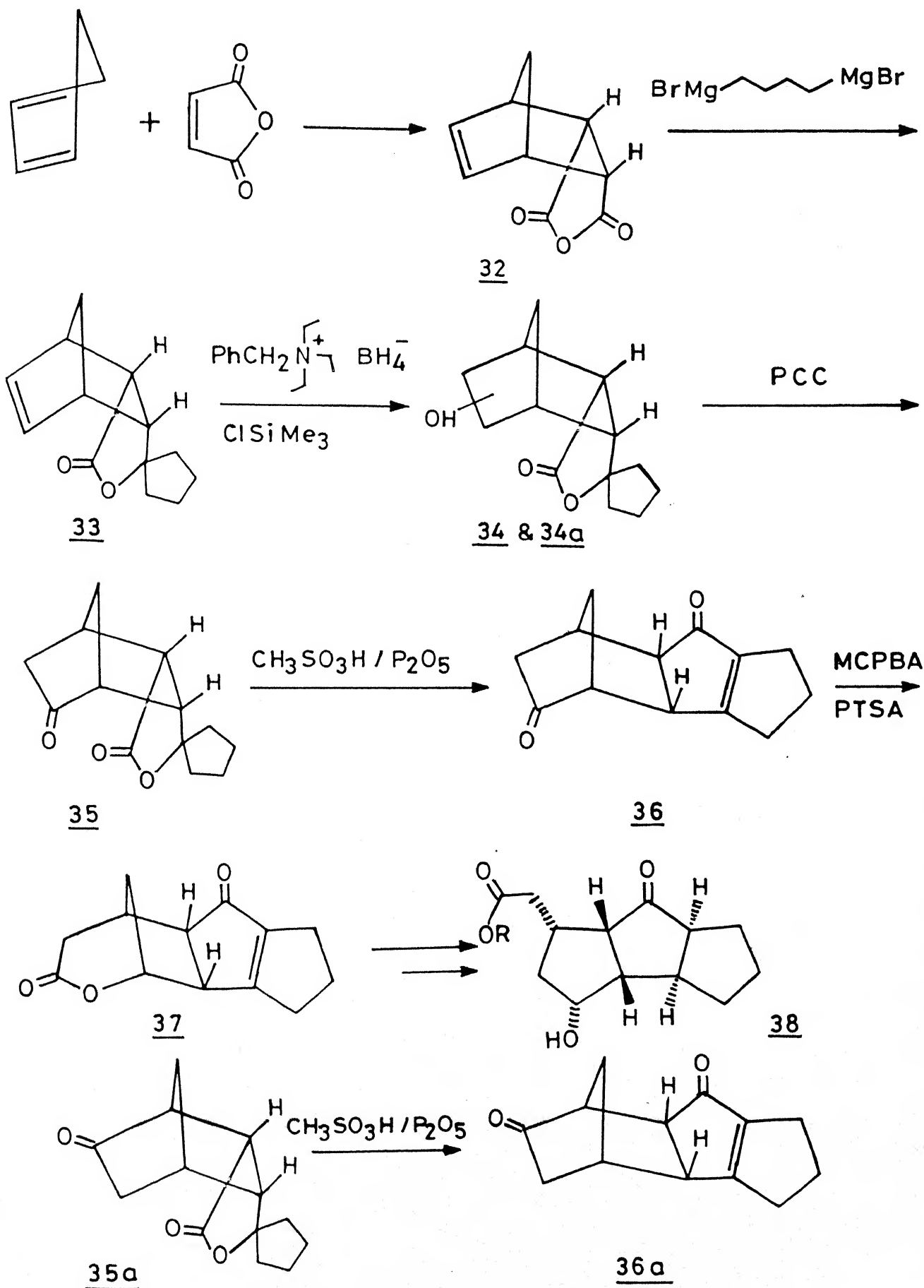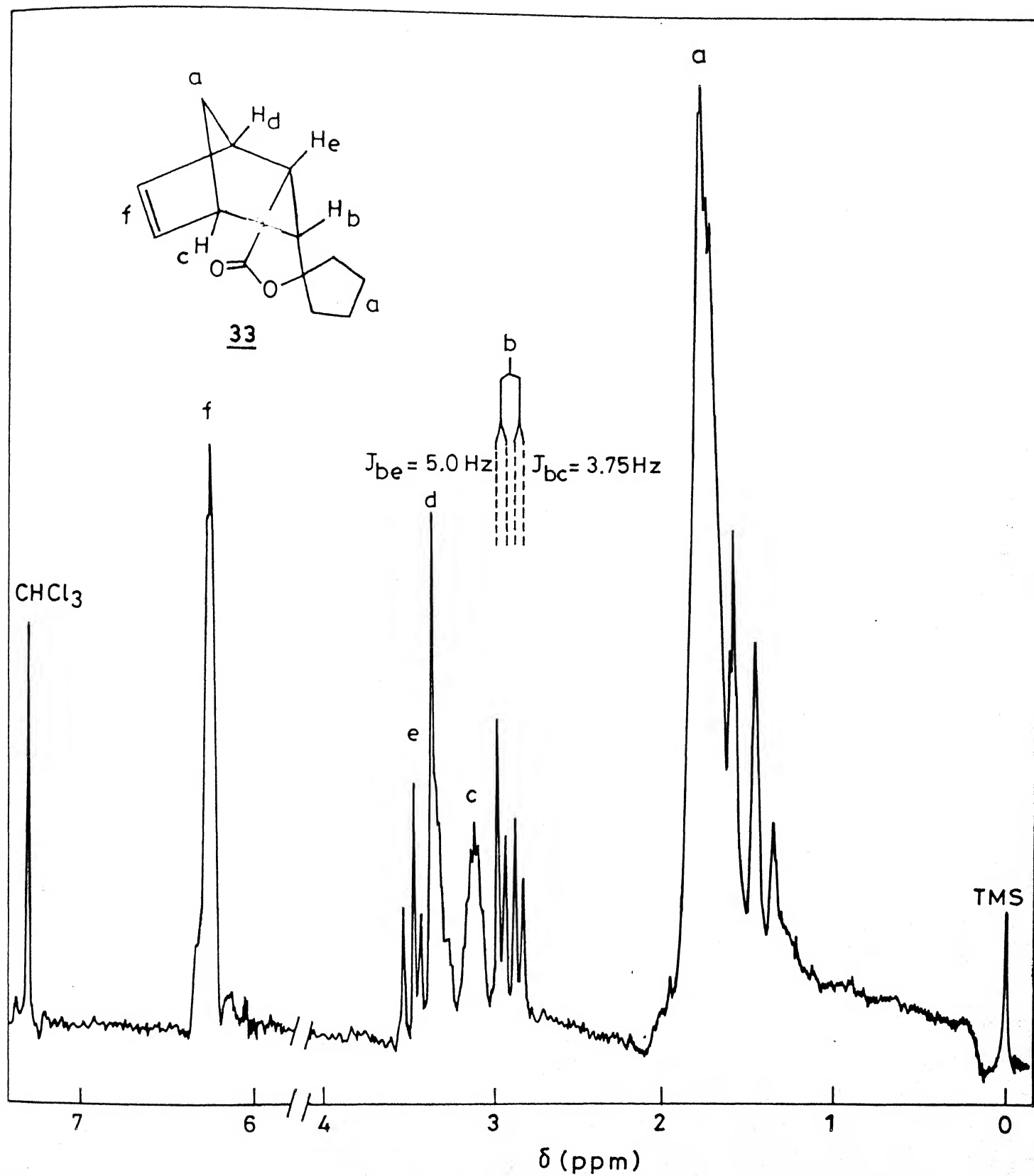
^{1}H NMR spectrum (80 MHz) of 33 .
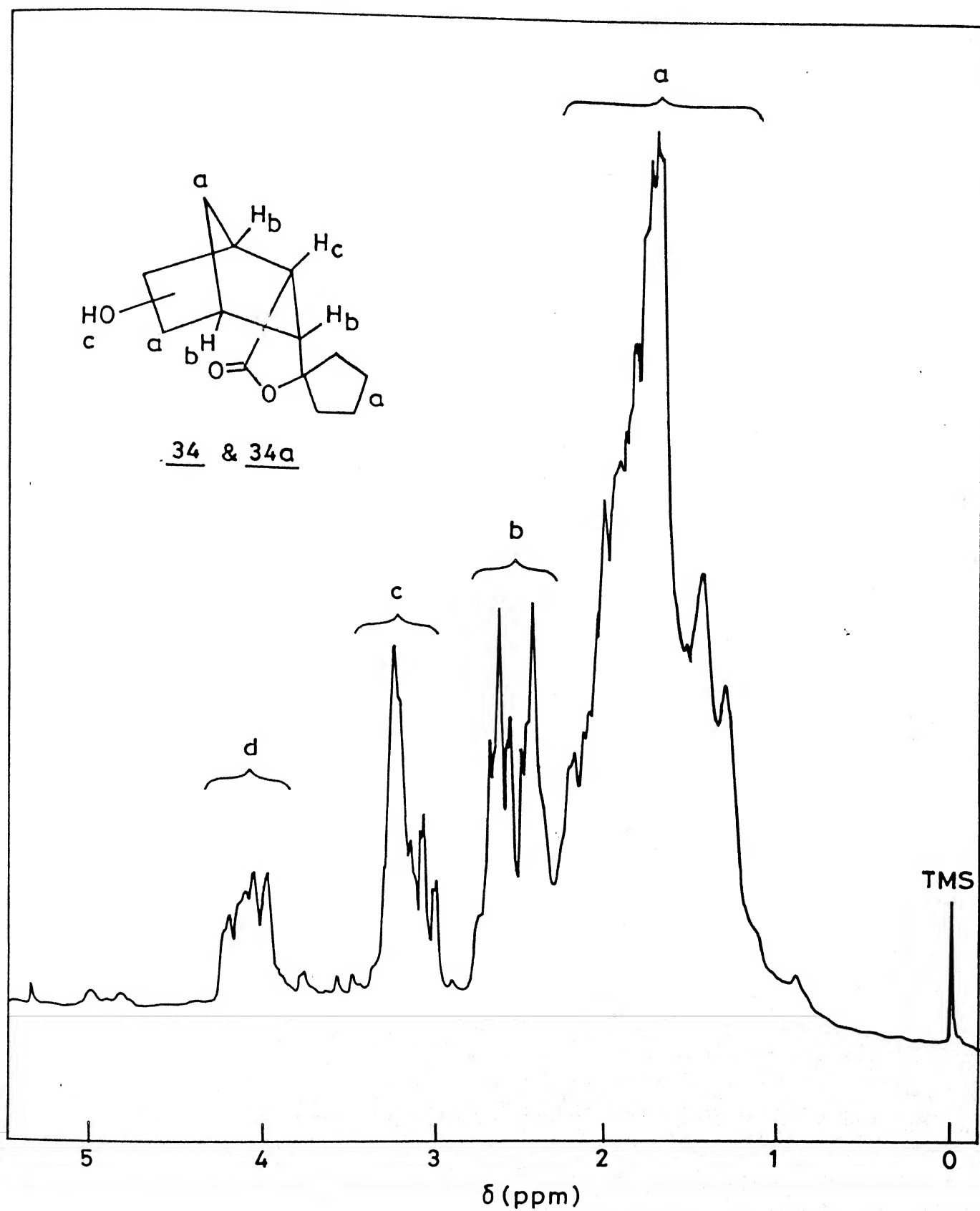
^{1}H NMR spectrum (80 MHz) of <u>34</u> & <u>34a</u>.
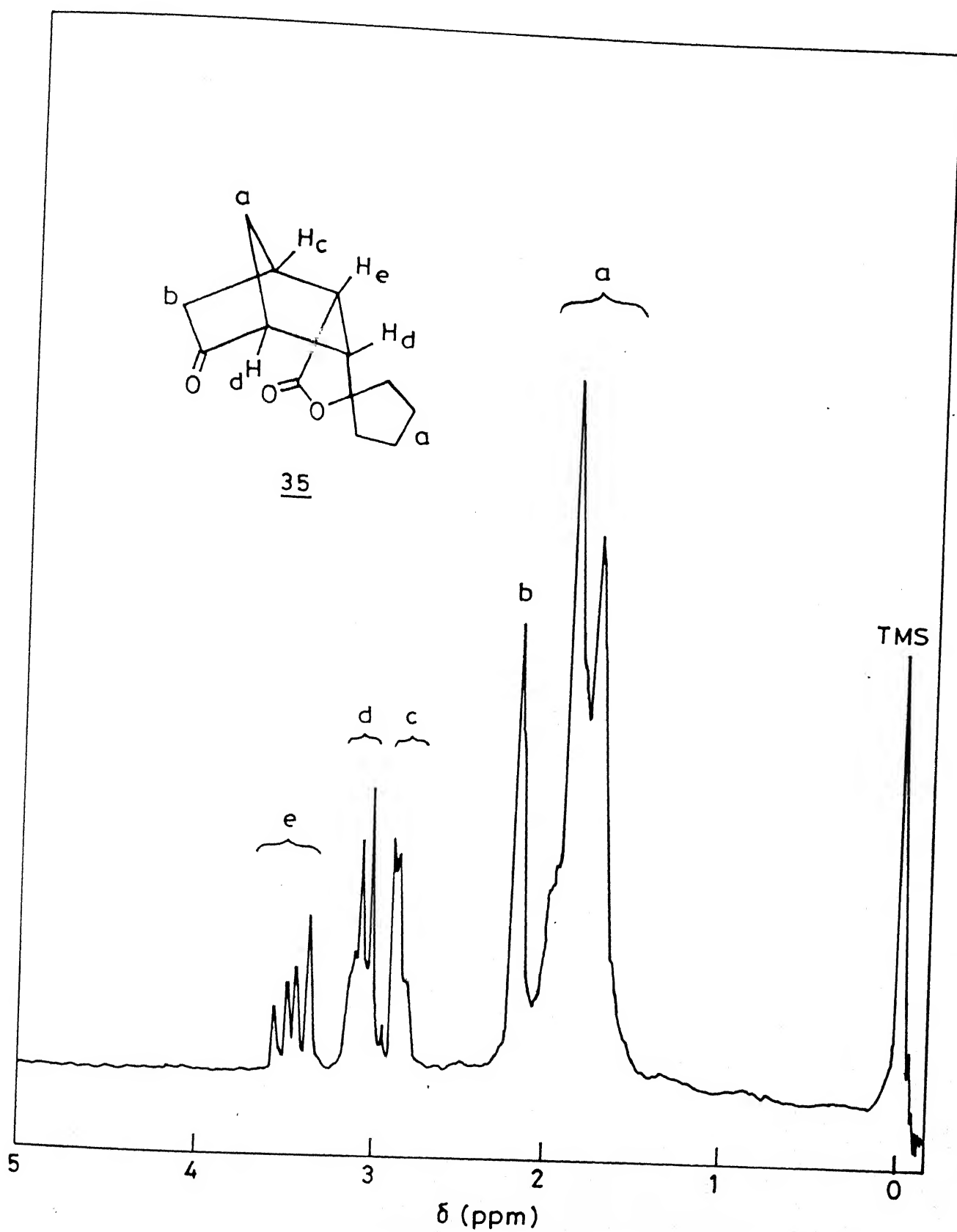
^{1}H NMR spectrum (80MHz) of 35 .
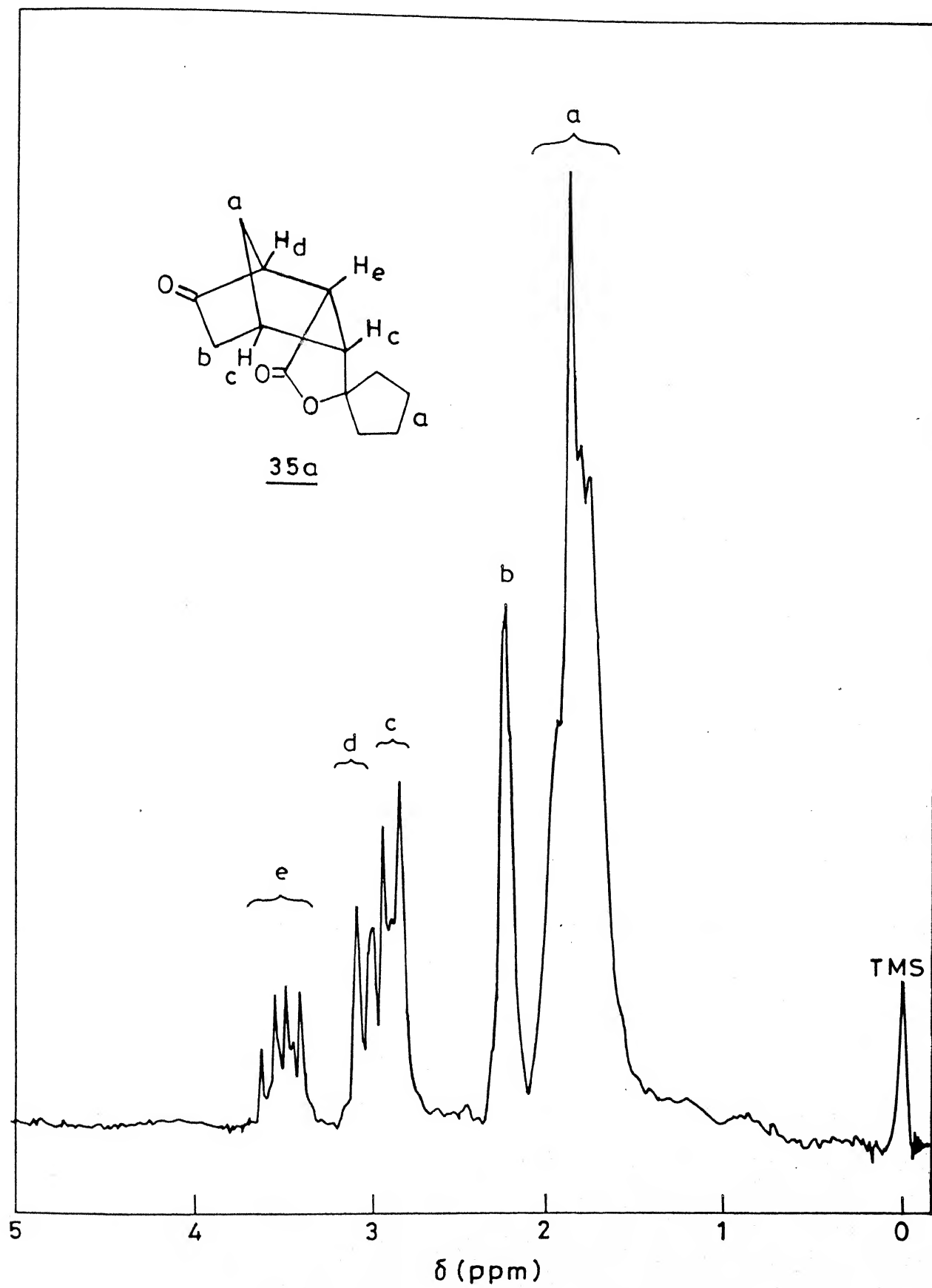
^{1}H NMR spectrum (80MHz) of 35a .

this stage the ketolactones 35 and 35a could be separated by flash chromatography. The isomeric ketolactones 35 and 35a were then treated separately with P_2O_5/methane sulfonic acid at 25°C for 2 h to afford the keto enones 36 and 36a respectively in 54% yield.[32] At this stage one of the ketoenones 36 was treated with m-chloroperbenzoic acid to afford 37 in 78% yield. This lacto-enone 37 on hydrolysis followed by reduction of the double bond would afford the cis-anti-cis tricyclic skeleton 38.

II.2.c Intermolecular [2+2] cycloaddition approach (endo-dicyclopentadiene - dichloroketene route)

The third approach towards the construction of cis-anti-cis tricyclopentanoid carbon skeleton takes advantage of the readily available endo-dicyclopentadiene as the starting material. The synthetic strategy adopted in this route is depicted in Scheme II. A. 12.

Freshly distilled cyclopentadiene was allowed to dimerize at 0°C to obtain pure endo-dicyclopentadiene.[33] Treatment of this with dichloroketene generated in situ with dichloroacetyl chloride and triethylamine afforded the dichlorocyclobutanone 39 in 50% yield.[34] One carbon homologation of 39 with diazomethane yielded the dichloropentanone. 40[22] which when treated with zinc/ acetic acid gave the cis-anti-cis fused tetracyclic ketone 41[22] (67%). The norbornene double bond in 41 was oxidatively cleaved with $KMnO_4$/$CuSO_4$ to give the dialdehyde 42 (52%). This route thus constitutes a short stereo controlled approach to the basic
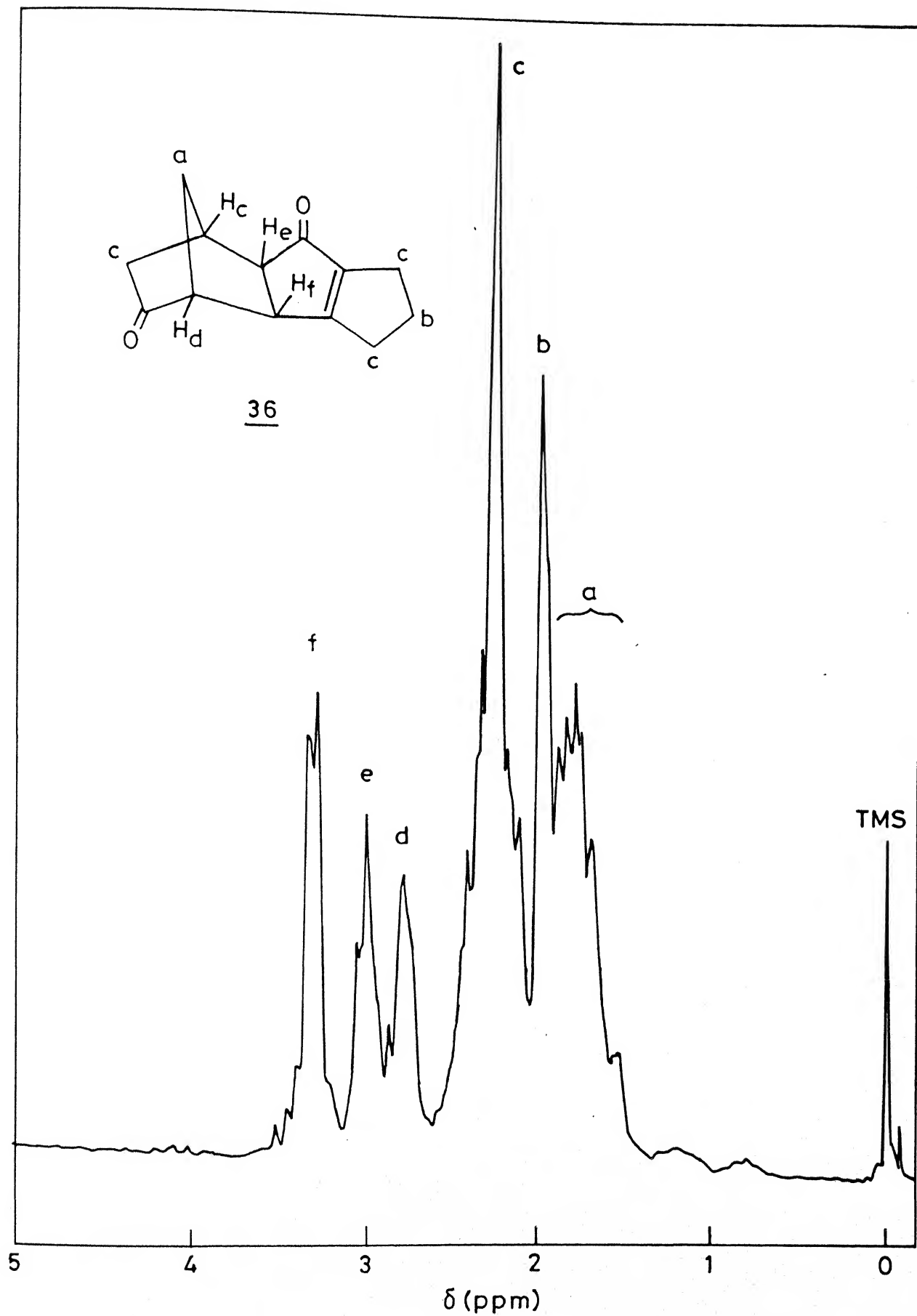
^{1}H NMR spectrum (80MHz) of 36 .
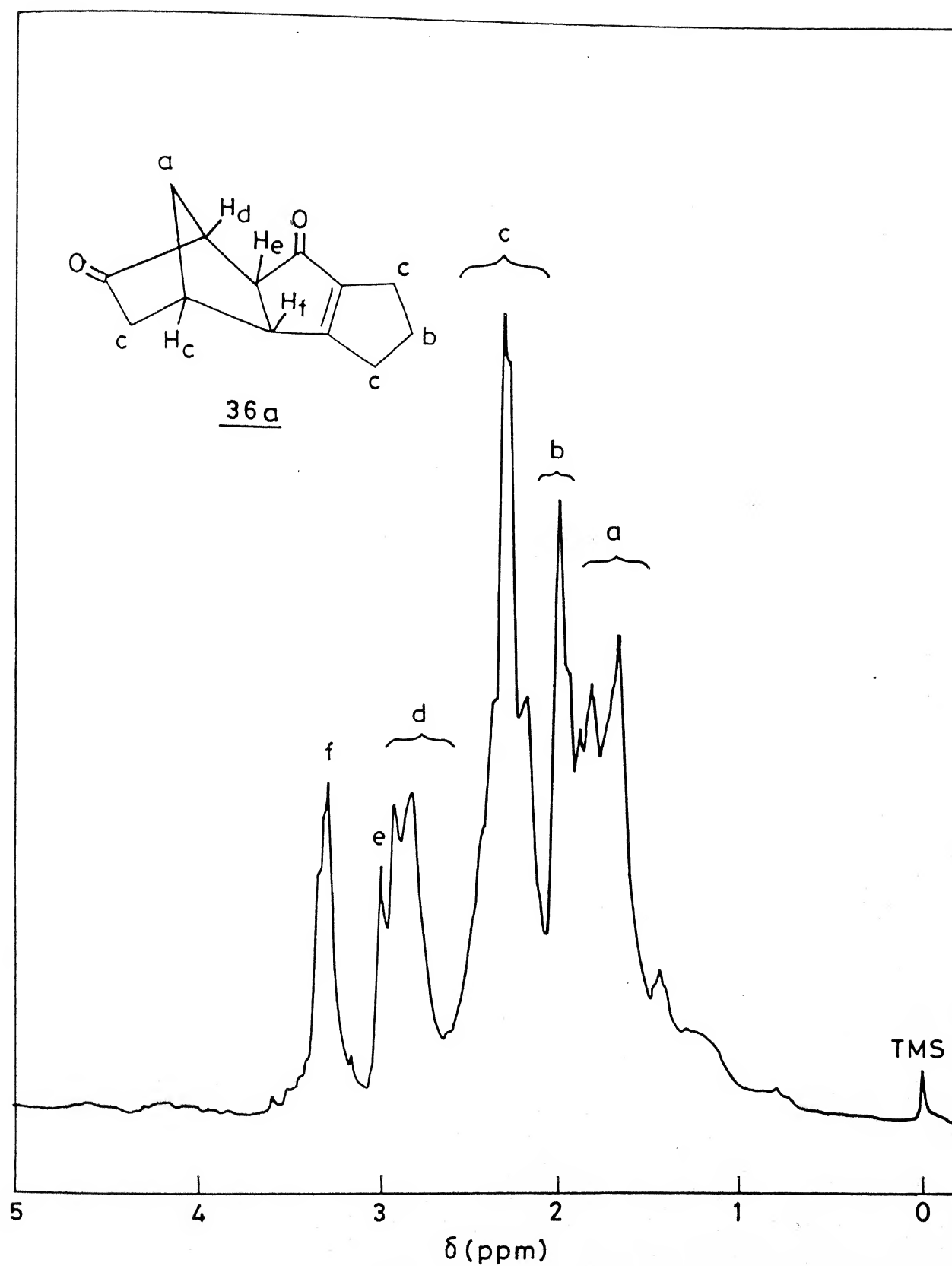
^{1}H NMR spectrum (80 MHz) of 36a .
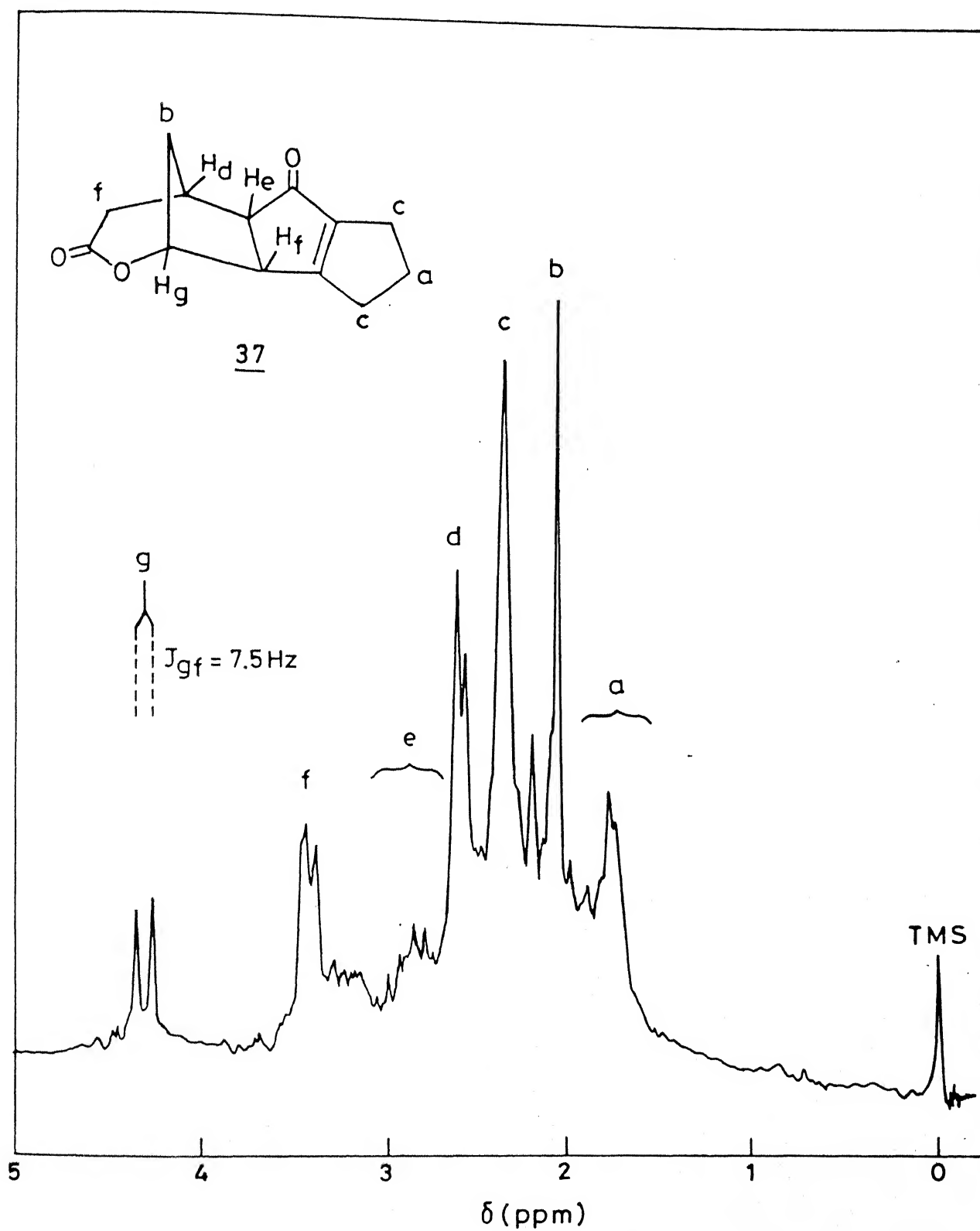
^{1}H NMR spectrum (80MHz) of **37** .

SCHEME II.A.12
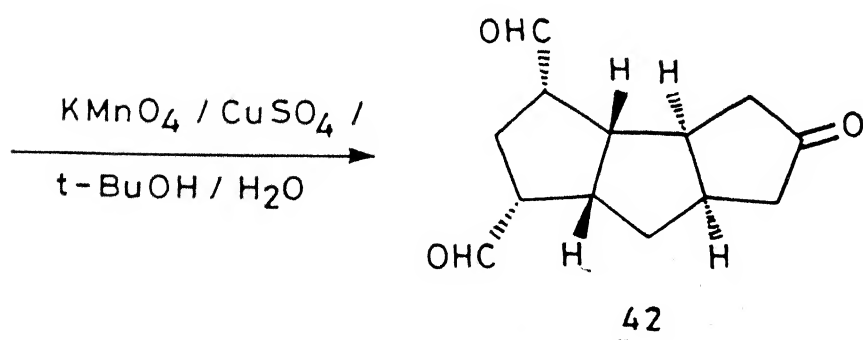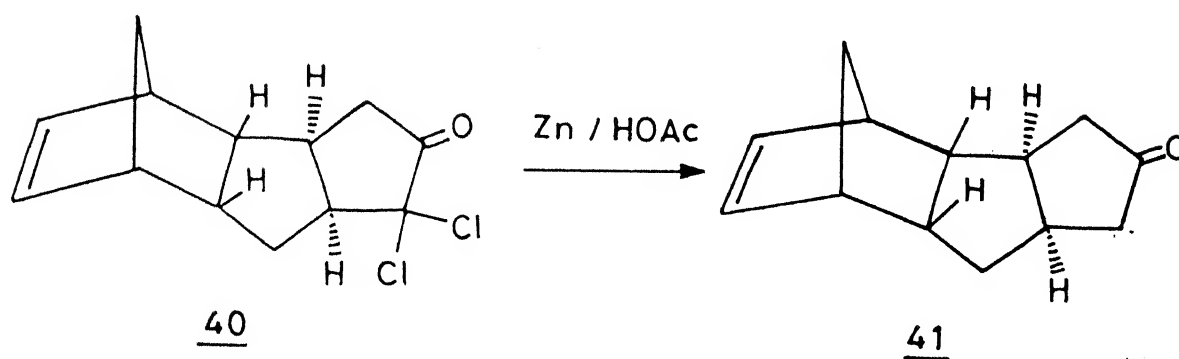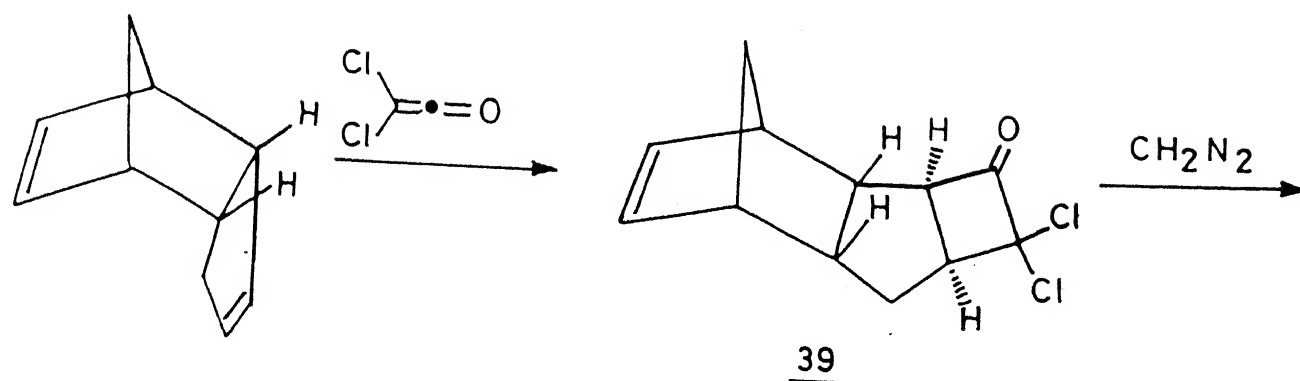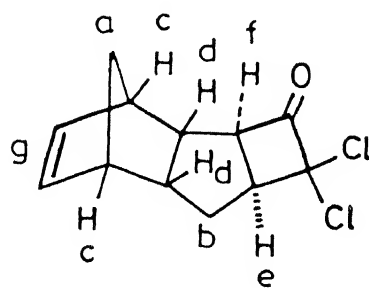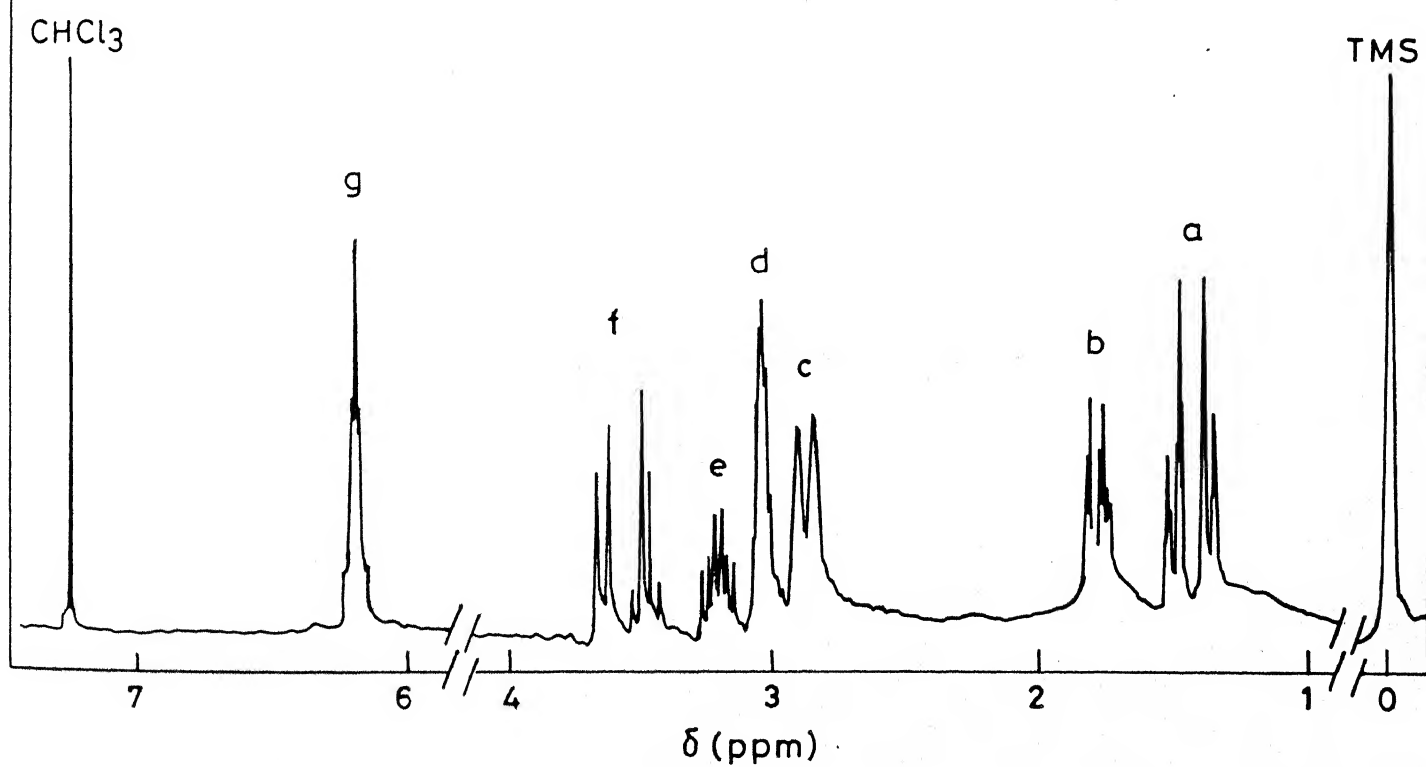
^{1}H NMR spectrum (200 MHz) of **39**.
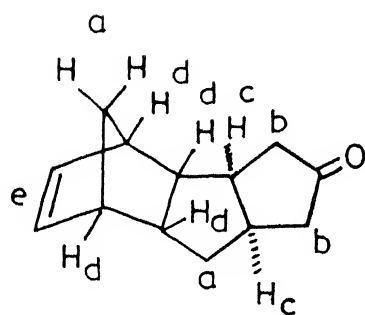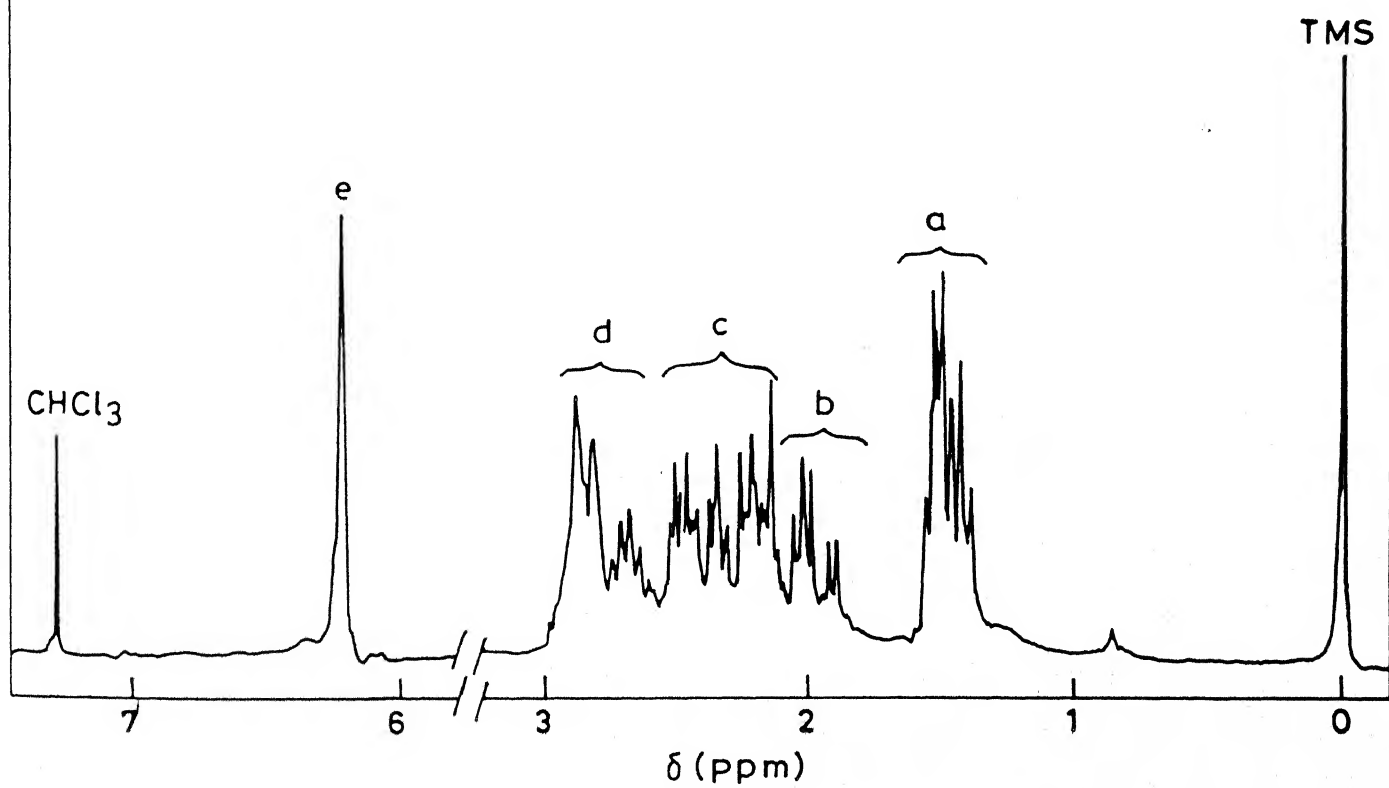
^{1}H NMR spectrum (200 MHz) of <u>41</u> .

cis-anti-cis tricyclopentanoid carbon skeleton from endo-dicyclo-pentadiene.

II.2.d Intramolecular vinylketene-olefin cycloaddition approach

Background

There have been some interesting observations in the chemistry of vinyl ketenes and their intramolecular [2+2] cyclo-addition to alkenes. For example Bedoukian and Wolinsky[34] have shown that treatment of geranoyl chloride 43 with triethylamine and methanol in benzene gave methyl γ-geranoate 45 in 85% yield presumably via the intermediacy of vinyl ketene 44 (Scheme II. A. 13). This precedent suggested that vinyl ketene 44 would be selectively formed in preference to vinyl ketene 46 from 43.

Snider and coworkers[14] have made use of this vinyl ketene in an intramolecular cycloaddition reaction. It was observed that the major product of cycloaddition was the bicyclic ketone 50 (Scheme II. A. 13). On the other hand Beereboom[8a,b] and Erman[8c] had earlier shown that treatment of geranic acid 48 with acetic anhydride and sodium acetate at reflux gave a 28% yield of fili-folone 52 (Scheme II. A. 14). They proposed 48 is converted to the mixed anhydride 49, which loses acetic acid to give 46, cycli-zing to give chrysanthenone 51. Under the reaction conditions chrysanthenone 51 is not stable but rearranges to filifolone 52 by a series of Wagner-Meerwein shifts initiated by protonation of the carbonyl group. Thus the apparently selective formation of

SCHEME II.A.13[34]
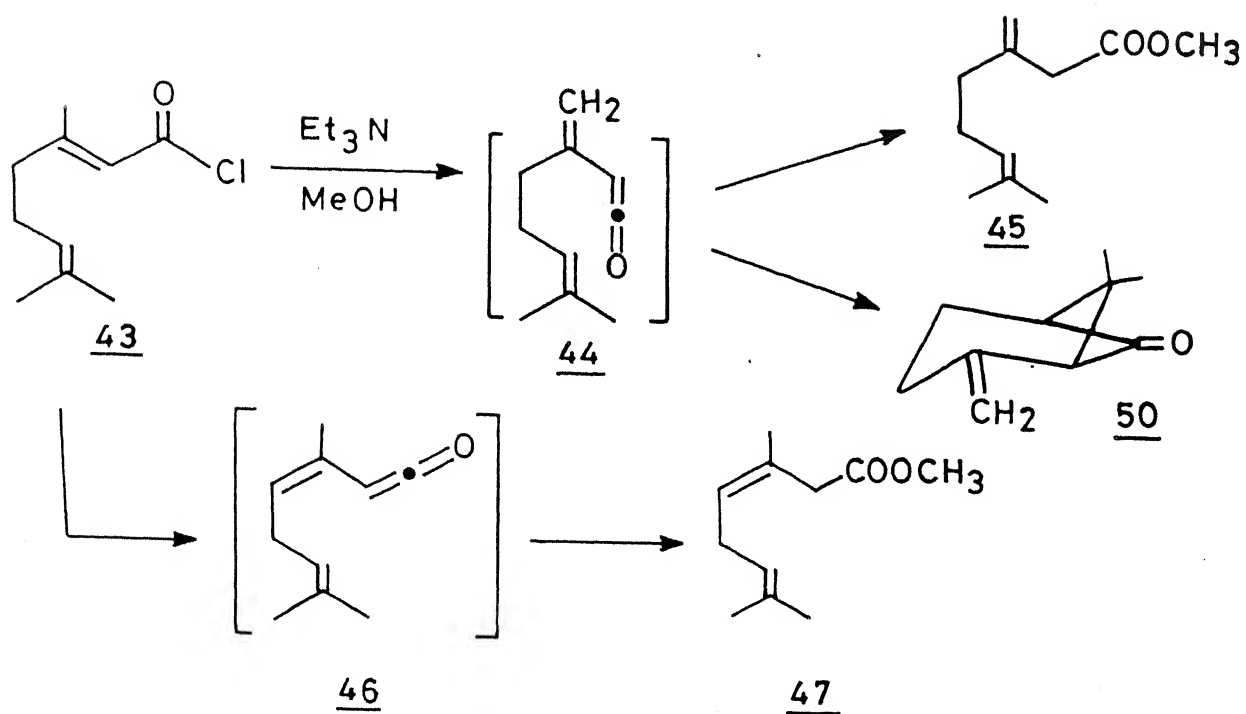
SCHEME II.A.14[8a-c]
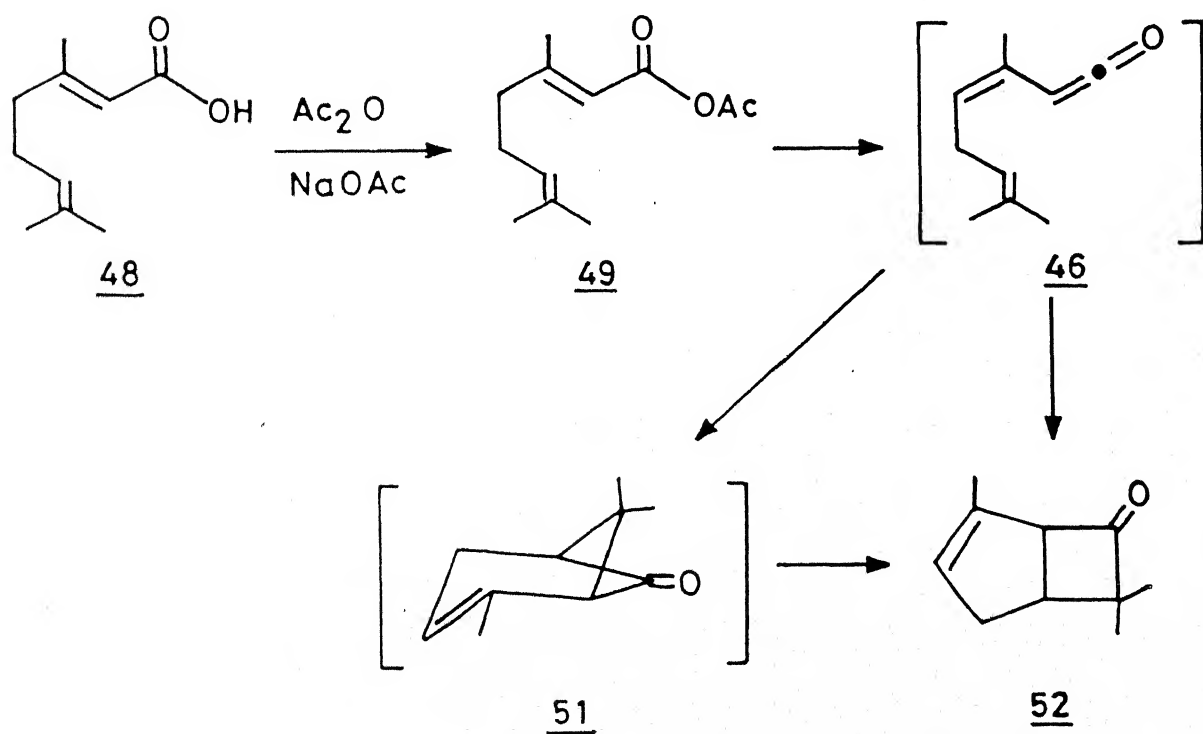
vinyl ketene 46 from the mixed anhydride 49 and vinyl ketene 44 from acid chloride 43 is puzzling. Snider[14] has tried to rationalise these observations as follows. The formation of vinylketene 44 from 43 is probably irreversible, since under the reaction conditions triethylamine hydrochloride precipitates out from the solution. The formation of vinylketene 46 from 48 in a mixture containing acetic acid is probably readily reversible. The cyclization of vinylketene 46 to 51 may be faster than the cyclization of 44 to 50. With this kind of background information on the regioselective deprotonation and generation of vinylketenes we decided to take advantage of this and develop a simple strategy for the construction of linearly fused triquinane skeleton through the intermediacy of a bicyclo[3.2.0]heptane framework.

II.3. Results and Discussion

It was anticipated that if a general methodology can be worked out for the construction of a bicyclo[3.2.0]heptane skeleton via the intramolecular vinylketene-olefin cycloaddition, it would be an easy access to the tricyclopentanoid natural product like hirsutene 3. The key features of such a strategy are depicted in the retro synthetic analysis (Scheme II. A. 15).

The bicyclic hydrocarbon 59 is the key intermediate in the synthesis of (±) hirsutene reported by Greene[4], which in turn can come from bicyclic ketone 58. Cyclobutanone 57 would then be an important intermediate for the synthesis of 58. It is for the

synthesis of <u>57</u> we planned to develop a general methodology involving regioselective formation of the vinylketene <u>56</u> from unsaturated carboxylic acid <u>55</u>.

The synthetic scheme which finally culminated in the synthesis of bicyclic ketone <u>57</u> from acid <u>55</u> is outlined in (Scheme II. A. 16).

5-Hexen-2-one <u>53</u> was synthesised by alkylation of acetylacetone with allylbromide[35]. Wittig reaction of ketone <u>53</u> with the ylid derived from triphenylphosphine and ethyl bromoacetate yielded the unsaturated carboxylic ester <u>54</u> as a mixture of geometric isomers.[13] Hydrolysis of the ester <u>54</u> afforded the unsaturated carboxylic acid <u>55</u>. A variety of reaction conditions for the generation of vinylketene <u>56</u> from carboxylic acid <u>55</u> were tried. In order to achieve regioselective deprotonation to get the desired vinylketene, reagents and reaction conditions were chosen in such a way a mixed anhydride intermediate would be formed under equilibrating conditions.

Initially the unsaturated carboxylic acid was treated under conditions reported earlier by Beereboom[8b]. This involved heating <u>55</u> with acetic anhydride and sodium acetate to form the mixed anhydride <u>60</u> which then can lead to the vinylketene <u>56</u> and an intramolecular [2+2] cycloaddition should lead to the key bicyclic intermediate <u>57</u>. When the reaction was done in refluxing benzene for 24 h the desired bicyclic ketone <u>57</u> was obtained in 15% yield after chromatographic purification. This compound <u>57</u>

SCHEME II.A.15

3   **59**   **58**

57   **56**   **55**

SCHEME II.A.16

53   **54**

55   **57**   **58**   **3**
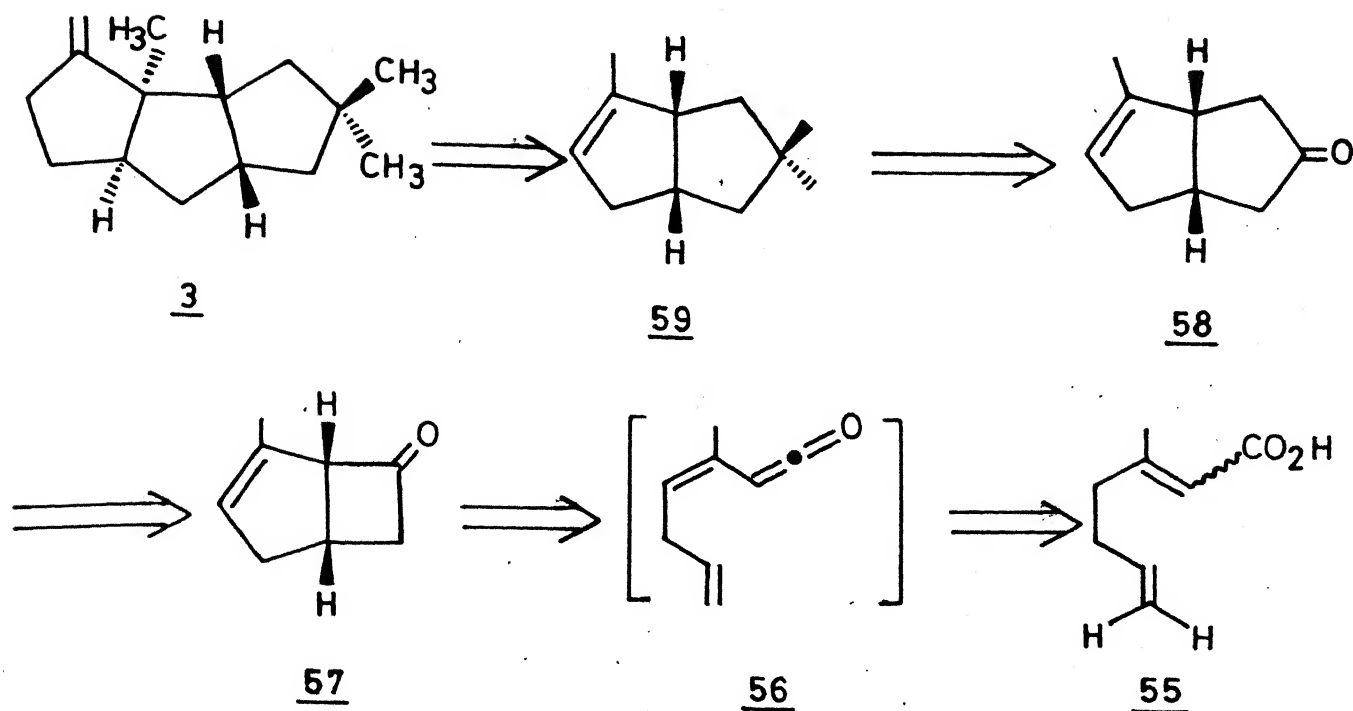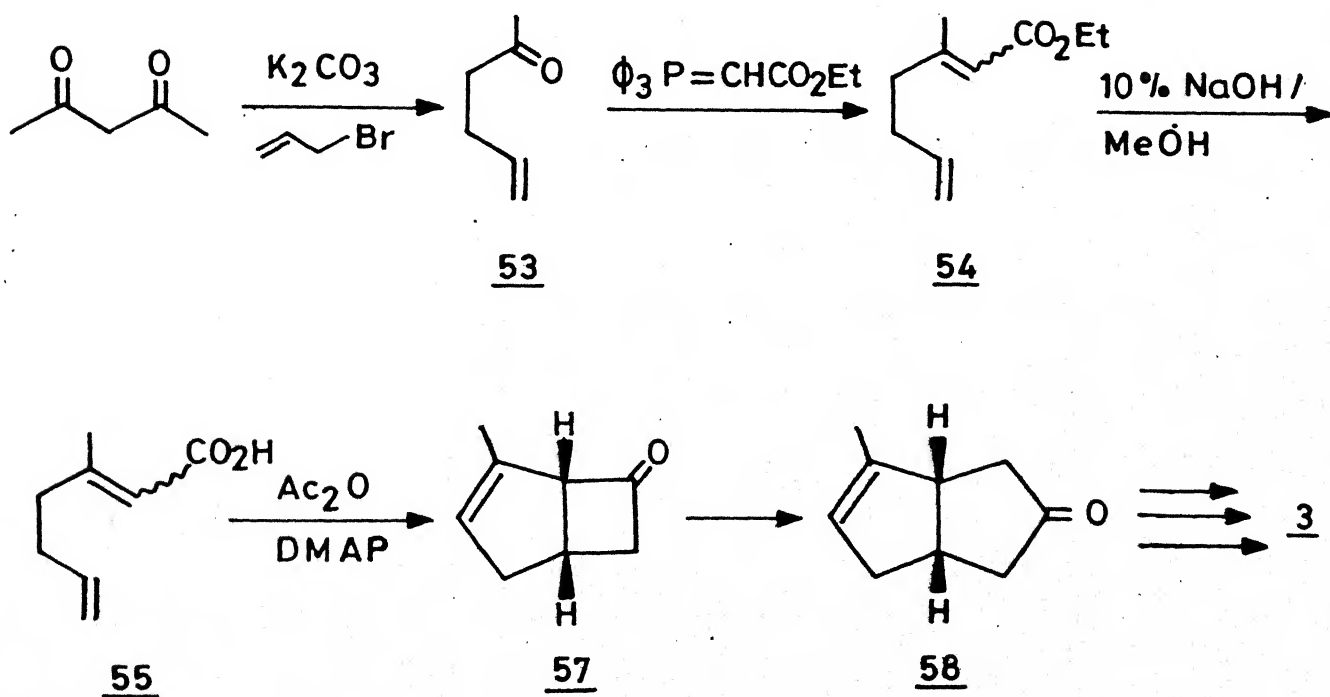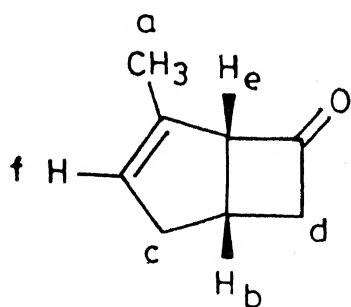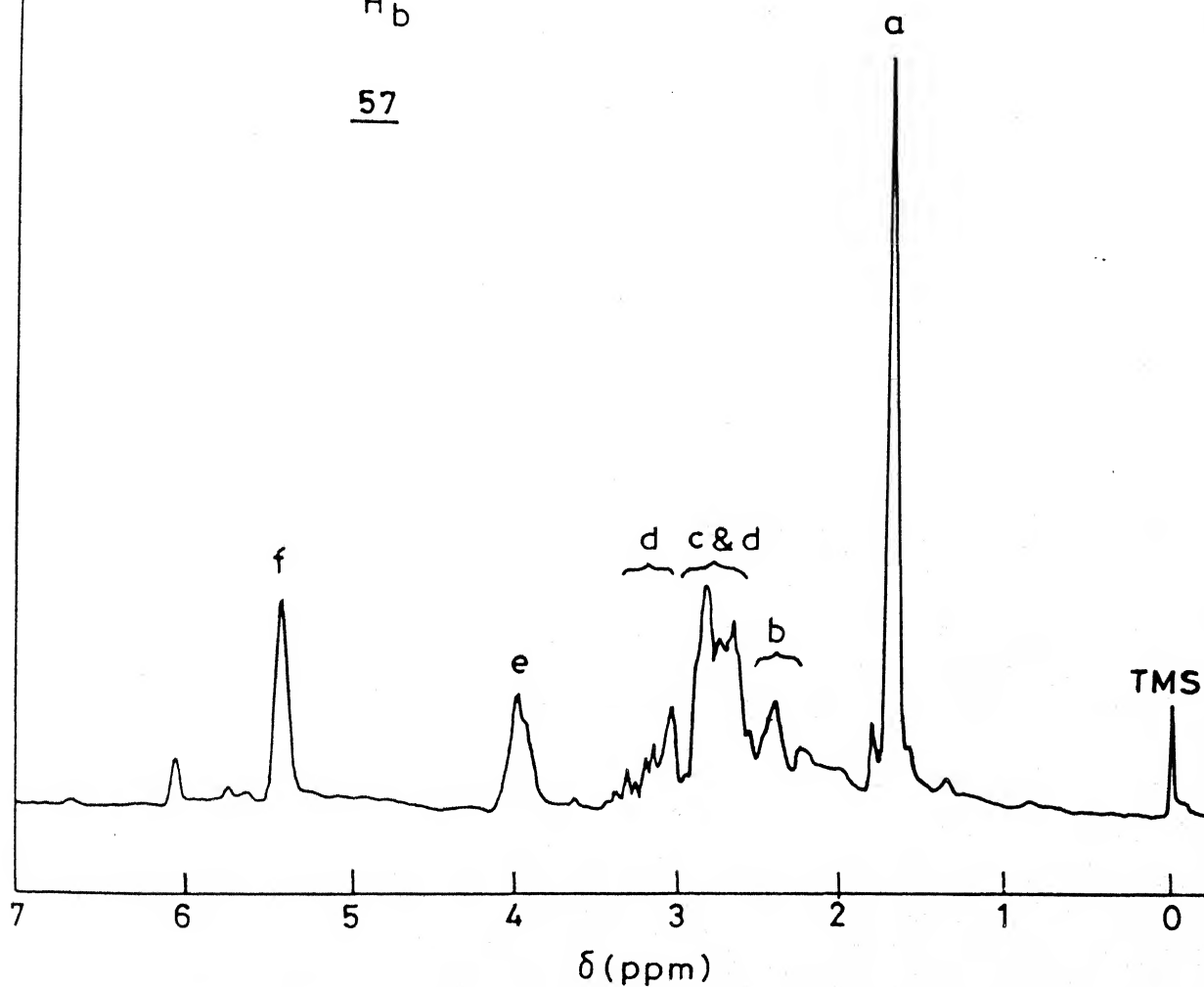
^{1}H NMR spectrum (80 MHz) of 57 .

showed IR absorptions at 3080, 1780 and 1640 cm^{-1} and had ^{1}H NMR absorptions at 1.68 (3H), 2.36 (1H), 2.5-2.84 (3H), 3.0-3.4 (1H), 4.0 (1H), 5.56 (1H). The mass spectrum showed the molecular ion at 122 (M^+).

When the reaction of the acid 55 was performed with two equivalents of acetic anhydride and two equivalents of dimethyl-aminopyridine in benzene under reflux for 16 h the cycloadduct 57 was formed in 27% yield.

Treatment of the acid 55 with acetic anhydride (10 eq) and 4-dimethylamino pyridine (1.5 eq) in benzene under refluxing condition, for 16 h afforded the bicyclic ketone 57 in 51% yield after chromatographic purification. Further modifications in the reaction conditions (higher temperature, change of solvent to toluene and longer reaction time) did not improve the yield of 57. Attempted reaction of acid 55 with trifluoroacetic anhydride in place of acetic anhydride did not give any of the desired product. A reaction was also performed under conditions reported recently by Ernst,[16] wherein the methyl ester 61 was refluxed in toluene with two equivalents of diisopropylethylamine and 1.5 equivalents of 4-dimethylaminopyridine. However, only the star-ting material was recovered.

It appears then that the formation of vinylketene 56 from 55 and the subsequent cycloaddition takes place reasonably well when the reaction of 55 is performed with excess acetic anhydride and

1.5 eq. of 4-dimethylaminopyridine in refluxing benzene for 18 h. Thus this simple methodology for the conversion of 55 to 57 would be a useful technique for the construction of the basic bicyclo[3.2.0]heptane carbon skeleton. Some preliminary experiments were carried out for the regioselective ring expansion of 57 to 58 with diazomethane[23,26] and 1-chloro-2-(methyl sulfinyl) benzene followed by rearrangement[36] but the desired product 58 could not be isolated. When the ring expansion of 57 to 58 is achieved, Reetz reaction[37] with dimethyl titanium dichloride can be applied to convert 58 to 59. This can then constitute a formal synthesis of (+) hirsutene.[4]

There is much scope for this methodology to be used for the regioselective generation of vinylketene from unsaturated carboxylic acids and its subsequent reactions in organic synthesis.

II.4 Experimental

General Procedures

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, tlc, m.p.).

Materials

Commercial grade solvents were distilled prior to use. Benzene was dried over anhydrous calcium chloride, distilled over sodium wire and kept over sodium wire. Dimethoxyethane was dried

over sodium hydroxide pellets, distilled over calcium hydride and kept over sodium wire. Absolute ethanol was prepared by distilling the rectified spirit over calcium oxide followed by distillation over magnesium ethoxide. Anhydrous liquid ammonia was obtained by distillation from sodium. Methyl iodide[43], Diazald[38] and N-methyl morpholine N-oxide[24], were prepared by the reported procedures. Acetic anhydride was distilled over phosphorous pent oxide prior to use. Tetrahydrofuran and diethyl ether were distilled over lithium aluminium hydride prior to use. Petroleum ether fractions 60-80°C were used for chromatography.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) Ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200°C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and then reimmersion and heating to ca. 200°C.

Column chromatography was performed using 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel. Gas chromatographic analyses were carried out on a Shimadzu GC-9A unit.

Physical data

Melting points (m.p.) were determined with a Uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80 instrument. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) etc. Coupling constants are reported wherever necessary and are expressed in Hz. Mass spectra (MS) were recorded on a Jeol JMS-D 300 mass spectrometer. The principal molecular fragments are reported.

II.4.a Intermolecular [2+2] cycloaddition approach
(3-methylindene route)

Preparation of 3-methylindene 17

To a stirred solution of indene (11.252 g, 101.18 mmol, 11.8 mL) in dimethoxy ethane (DME) (100 mL) under nitrogen was added lithium (0.768 g, 110.68 mg atom) cut into small pieces and refluxed for 5-5.5 h. The dark red solution obtained was cooled

in an ice bath and methyliodide (27.26 g, 102.76 mmol, 12 mL) in dimethoxyethane (10 mL) was added over a period of 0.5-0.75 h. After the addition was complete the reaction mixture was stirred for a further 0.5 h. Excess lithium was carefully destroyed by adding 10% hydrochloric acid (50 mL) and extracted with ether (25 mL x 3). The ethereal layers were combined and washed successively with water, brine and dried over anhydrous magnesium sulfate. The crude product obtained after evaporation of the solvent was distilled under vacuum to get a mixture of indene, 1- and 3-methylindene. The product from two such reactions were mixed and refluxed with triethylamine (2 mL) for 2 h. Water (25 mL) was added and extracted with ether (75 mL). The ether extract was washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product obtained was fractionated under vacuum to yield unreacted indene (8.403 g b.p. 74-75°C/11mm) and 3-methylindene (10.986 g, 65%, b.p. 78-80°C/11 mm; lit.[18] b.p. 76-78°C/11mm). The purity of 3-methylindene was analyzed by gas chromatograph on a Shimadzu GC-9A instrument equipped with a flame ionization detector and a column (2 m, bonded OV-17). Temperature programming was as follows : Injection temperature 220°C, column temperature 120°C/min, raised at 5°C /min and isothermal stage at 160°C for 1 min. Flow rate for N_2 60 mL/min, H_2 50 mL/min and air 200 mL/min. Indene t_R 2.925 min, 3-methylindene t_R 4.42 min.

^{1}H NMR (CCl$_4$)   : 2.22 (m, 3H, CH$_3$), 3.27 (t, 2H, CH$_2$),

6.12 (m, 1H, =CH-CH$_2$), 7.17 (m, 4H).

Preparation of 2-chloropropionylchloride[22]

To a stirred solution of 2-chloropropionic acid (40.32 g, 0.371 mmol, 35 mL) and DMF (2 mL) at 85°C was added dropwise thionylchloride (53.042 g, 0.446 mole, 32.5 mL) over a period of 0.5-0.75 h. After the addition was complete, the reaction mixture was stirred at this temperature for 2 h. The temperature was lowered and the product was distilled at atmospheric pressure (100-115°C) to yield. 2-Chloropropionyl chloride (40.151 g, 85%) [lit.[40] b.p. 110°C/744 mm]

Preparation of 3,4-Benzo-5,6-dimethyl-6-chlorobicyclo[3.2.0]-heptan-7-one 18

3-Methylindene 17 (2.224 g, 17.11 mmol) and triethylamine (1.904 g, 18.82 mmol, 2.6 mL) were taken in petroleum ether (40-60°C, 80 mL) and gently refluxed. To this 2-chloropropionyl chloride (2.03 g, 16 mmol, 1.55 mL) in petroleum ether (40-60°C, 16 mL) was added dropwise over a period of 0.5 h. After the addition was over, it was refluxed for an additional two hours. The reaction mixture was allowed to come to room temperature and water (20 mL) was added and extracted with three (25 mL) portions of ether. The ethereal layers were combined and washed with water (20 mL) and brine (25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product thus obtained was purified by flash chromatography over silica gel (2% ether in petroleum ether) to recover unreacted starting material 17 (0.7 g). Further elution (5% ether in petroleum ether) afforded the adduct 18 (1.86 g, 72%) as a yellow solid.

m.p.   : 64-65°C.

IR (KBr)   : 3070, 2940, 1780 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.33 (s, 3H), 1.75 (s, 3H), 3.13-3.24 (m, 2H,

3.94-3.99 (dd, 1H), 7.23-7.26 (m, 4H, aromatic).

^{13}C NMR(CDCl$_3$) : 21.1, 33.1, 33.6, 55.8, 82.5, 125.68, 125.73,

127.5, 128.4, 142.98, 144.2, 206.96.

Ms (m/e)   : 222, 220, 203, 185, 177, 158, 157.

Anal. for

C$_{13}$H$_{13}$OCl : Calcd. C, 70.75; H, 5.89.

Found C, 70.54; H, 5.68.

Preparation of 3,4-Benzo-5,6-dimethyl-6-chlorobicyclo[3.3.0]-octan-7-one 19

Diazomethane was generated by the reported procedure[38] from Diazald (4.28 g) and added in portions to a stirred solution of 18 (1.86 g, 8.435 mmol) in ether (5 mL) at 0°C and was allowed to raise to room temperature. The reaction was monitored periodically by TLC (1-2 h). Excess diazomethane was destroyed by the addition of acetic acid (4-5 drops). Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with (2X25 mL) portions of ether. The combined ethereal layers were washed with saturated sodium bicarbonate solution (10 mL), brine (20 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product thus obtained was used in the next step without further purification.

IR (neat)   : 3060, 2930, 2850, 1755 cm^{-1}.

Preparation of 3,4-Benzo-5,6-dimethylbicyclo[3.3.0]octan-7-one 20

Compound 19 (1.9 g, 8.10 mmol) in acetic acid (14 mL) was treated with zinc powder (4 g) and heated at 70°C for 1.5 h. After allowing the reaction mixture to cool to room temperature ether (30 mL) and water (15 mL) were added and the layers were separated. The aqueous layer was extracted with two portions of ether (25 mL) and the combined organic layers were successively washed with aqueous sodium bicarbonate solution (15 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulfate. The crude product obtained on evaporation of the solvent was purified by flash chromatography (10% ether in petroleum ether) over silica gel to afford 20 (1.58 g, 97.5%) as an oil.

IR (neat) : 3045, 3020, 2960, 2930, 1740 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.07 (d, 3H, CH$_3$, J=7Hz), 1.22 (s, 3H, CH$_3$), 2.3 (q, 1H), 2.58 (dd, 2H), 2.76 (m, 1H), 2.76, 3.31 (m, 2H, AB- part of an ABX$_n$), 7.22 (m, 4H).

^{13}C NMR (CDCl$_3$) : 8.1 (q), 22.1 (q), 22.8 (q), 30.1 (s), 35.8 (t), 37.4 (t), 48.0 (d), 51.4 (d), 70.9 (t), 72.8 (t), 122.7(d), 124.9(d), 126.4(d), 126.7(d), 140.98(s), 153.4(s), 219.6(s).

Ms (m/e) : 200(M$^+$), 157, 143, 130.

Anal. for

C$_{14}$H$_{16}$O : Calcd. C, 84.00; H, 8.00

Found C, 83.80; H, 7.74.

Preparation of ethylene ketal <u>21</u>

To a stirred solution of <u>20</u> (1.722 g, 8.61 mmol) and ethy-
lene glycol (0.588 g, 9.47 mmol, 0.33 mL) in dry benzene (120 mL)
was added catalytic amount of p-toluene sulfonic acid (20 mg) and
refluxed using a Dean Stark separator. When no more azeotrope
formation was observed (1.5 h) saturated sodium bicarbonate solu-
tion (20 mL) was added and the layers were separated. The
aqueous layer was extracted with ether (25 mL) and the combined
organic layers were successively washed with water, brine and
dried over anhydrous sodium sulfate. The solvent was evaporated
and the crude product thus obtained, was purified by flash chro-
matography over silica gel (ether : petroleum ether, 1:9) to get
<u>21</u> (1.749 g, 83%).

IR (neat)   : 3060, 2940, 2870, 1635 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 1.16 (d, 3H, CH$_3$, J= ~10Hz), 1.25 (s, 3H,CH$_3$)
                     1.28-1.75 (m, 3H), 2.0-2.33 (m, 1H), 2.73-3.50
                     (m, 2H), 3.94 (m, 4H), 7.25 (m, 4H).

^{13}C NMR (CDCl$_3$) : 12.5, 22.7, 30.2, 31.5, 37.8, 39.4, 47.6, 64.7,
                     65.0, 118.5, 124.98, 125.1, 126.5, 126.7,
                     143.1, 153.1.

Birch reduction of <u>21</u>

Lithium pieces (0.746 g, 107.5 mg atom) were added over a
period of 0.25 h to a stirred solution of redistilled liquid
ammonia (100 mL). To this ethylene ketal <u>21</u> (1.749 g, 7.168
mmol) in tetrahydrofuran (10 mL) and absolute ethanol (0.9 mL),

was added and stirring was continued. When the blue colour of the solution disappeared (4 h) solid ammonium chloride was carefully added until excess lithium got destroyed. Ammonia was allowed to evaporate at room temperature. The curdy white precipitate was dissolved in water and extracted with ether (2x30 mL). The ethereal extracts were washed with brine until the washings were neutral to litmus and dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product thus obtained, was purified by flash chromatography (ether : petroleum ether, 1:9) to afford 22 (1.728 g, 98.8%) as an oil.

IR (neat)   : 3020, 2920, 2870, 1115, 1050 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 0.84 (d, 3H, CH$_3$, J=7.5Hz), 0.97 (s, 3H,CH$_3$)

1.12-1.48 (m, 3H), 1.86-2.19 (m, 3H), 2.61

(br s, 4H), 3.97 (m, 4H), 5.8 (br s, 2H).

Cis-Hydroxylation of 22 with osmium tetroxide and N-methyl morpholine N-oxide[24]

The olefin 22 (1.728 g, 7.02 mmol) and N-methyl morpholine-N oxide (1.317 g, 11.238 mmol) in acetone (40 mL) and distilled water (14 mL) were treated with a solution of osmium tetroxide (0.178 g in 1.8 mL of tetrahydrofuran, 0.7 mmol) and the resulting mixture was stirred at room temperature for 80 h. Ethylacetate (50 mL) and saturated sodium bisulphite solution (5 mL) were added and the two-phase mixture was stirred vigorously for 0.25 h. The organic layer was removed and the aqueous phase was extracted with ethyl acetate (4x50 mL); the combined organic

layers were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to afford a green viscous liquid. The crude product was purified by flash chromatography over silica gel (ether:petroleum ether 1:9) to afford the unreacted starting material 22 (0.3 g). Further elution (ethyl acetate :petroleum ether, 7:3) afforded the diol 23 (1.269 g, 78%) as a viscous oil.

IR (neat) : 3500, 2920, 1640 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 0.88 (d, 3H, CH$_3$ J=7.5 Hz), 1.0 (s, 3H, CH$_3$), 1.12-1.31 (m, 3H), 1.81-2.06 (m, 1H), 2.24 (m, 6H), 3.25 (br, 2H), 3.94 (m, 6H).

^{13}C NMR (CDCl$_3$) : 8.8, 19.5, 30.6, 30.9, 39.6, 39.9, 40.8, 41.8, 45.9, 64, 64.2, 68.8, 69.1, 117.7, 137.9, 138.1.

Ms (m/e) : 280(M^+), 164, 146, 101.

Anal. for

C$_{16}$H$_{24}$O$_4$: Calcd. C, 68.57; H, 8.57.

Found C, 68.42; H, 8.38.

Catalytic reduction of diol 23

Diol 23 (1.269 g, 4.53 mmol) in dry methanol (5 mL) was added to activated Adam's catalyst (60 mg) in dry methanol (10 mL) and was hydrogenated at a hydrogen pressure of 60 psi for 1 h in a high pressure hydrogenation vessel. The crude product was filtered over a small pad of Celite and fresh Adam's catalyst (60 mg) was added and the hydrogenation was allowed to go for an additional hour at 60 psi. The catalyst was filtered off and the

filtrate was concentrated to get a highly viscous oil which was homogeneous to TLC. The crude diol thus obtained was purified by flash chromatography (ethyl acetate : petroleum ether, 7:3) to afford the diol 24 as a viscous oil (1.2 g, 94%) which was used in the next step.

Oxidative cleavage of diol 24 with lead tetraacetate

To a stirred solution of the diol 24 (0.104 g, 0.37 mmol) in dry benzene (3 mL) was added lead tetraacetate (0,195 g, 0.44 mmol) in small portions and the resulting mixture was stirred at room temperature for 5-10 min. The reaction mixture was diluted with ether (10 mL) and filtered through a pad of Celite and anhydrous magnesium sulfate. The filtrate upon concentration afforded the dialdehyde which was purified immediately over silica gel (ethyl acetate : petroleum ether, 4:6) to afford the dialdehyde 28 (0.08g, 91%).

IR (neat) : 2960, 2930, 2720, 1720 cm^{-1}.

^{1}H NMR (CDCl$_3$): 1.0 (d, 3H), 1.13-1.69 (m, 5H), 1.28 (s, 3H), 2.14-2.24 (m, 3H), 2.38-2.51 (m, 4H) 9.64 (t, 2H).

II.4.b Intermolecular [4+2] cycloaddition approach (cyclopentadiene-maleic anhydride route)

Preparation of cyclopenta-1,3-diene

Commercially available dicyclopentadiene (30 mL, endo/exo mixture) was taken in a dropping funnel attached to a 250 mL three necked round bottomed flask containing paraffin oil (75 mL).

A fractional distillation assembly with its receiver cooled in an ice bath was attached to the second neck. Ice-cooled water was circulated through the condenser. The paraffin oil was heated in an oil bath to $220^{\circ}C$ and dicyclopentadiene was added dropwise such that the rate of addition and the rate of condensation of cyclopenta-1,3-diene were nearly the same. After the addition was over (3 h) heating was continued for an additional 0.5 h. Cyclopenta-1,3-diene was obtained as a clear liquid and it was redistilled and used for the next step. Yield 15.932 g.

b.p. : $41-42^{\circ}C$ (lit.[38] b.p. $41.5-42^{\circ}C$).

Preparation of cis-endo-5-norborn-5-ene-2,3-dicarboxylic anhydride 32[39]

To a suspension of maleic anhydride (19.6 g, 0.2 mol) in dry benzene (20 mL) was added with vigorous stirring cyclopenta-1,3-diene (13.2 g, 0.2 mol, 16.7 mL) at $0-5^{\circ}C$. Maleic anhydride dissolved with the evolution of heat and a white crystalline solid separates out immediately. This was filtered over a Buchner funnel and was recrystallized from petroleum ether. Yield 30 g (96%).

m.p. : $162-163^{\circ}C$ (lit.[39] m.p. $164-165^{\circ}C$).

IR (KBr) : 3040, 2900, 1860, 1780, 1615 cm^{-1}.

Preparation of 1,4-dibromobutane[38]

A mixture of 125 g (85 mL) of 48 percent hydrobromic acid and 38 g (21 mL) of concentrated sulfuric acid was placed in a 250 mL round bottomed flask. Redistilled tetrahydrofuran (9 g,

0.125 mL, 10 mL) was added with stirring. A reflux condenser was attached to the flask and refluxed gently for 3 h. The lower layer of dibromide was separated and the aqueous layer was extracted with two 50 mL portions of ether. The combined organic layers were successively washed with water, 10% sodium carbonate solution and then dried over anhydrous magnesium sulfate. After evaporation of the solvent, the product was distilled to yield 1,4-dibromobutane (24 g, 89%).

b.p.   : $83^{\circ}C/12$ mm (lit.[38] b.p.$83-84^{\circ}C/12$ mm).

Preparation of 2',6'-endo-spiro[cyclopentane-1,5'-[4]oxatricyclo [5.2.1.0^{2,6}]dec-8'-en-3'-one] 33

The anhydride 32 (2.46 g, 15 mmol) in tetrahydrofuran (15 mL) was added at $-12^{\circ}C$ with stirring under nitrogen to 1,4-butanodimagnesium bromide (15 mmol) prepared from magnesium powder (0.875 g, 36 mg atoms) and 1,4-dibromobutane (3.24 g, 15 mmol, 1.79 mL) in tetrahydrofuran (20 mL). The reaction mixture was kept at this temperature for 3 h and then overnight at room temperature. After hydrolysis with (5-10%) hydrochloric acid and stirring for an additional hour at $40^{\circ}C$, the organic layer was separated, the aqueous layer was extracted with ether and the combined organic layers were washed with bicarbonate solution, brine and dried over anhydrous sodium sulfate. The solvent was evaporated to give the crude spirolactone 33, which was recrystallized from ether-petroleum ether to give 33 as white flakes 2.04 g (65%).

m.p.   : 70-71°C (lit.[28] m.p. 74-75°C).

IR (KBr)   : 3060, 2960, 2875, 1760 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.3-1.9 (m, 10H), 2.89 (dd, 1H, J=5 and 3.75 Hz)

3.11 (t, 1H), 3.37 (m, 1H), 3.39 (dd, 1H),

6.23 (br s, 2H).

Ms (m/e)   : 205(M+1), 139, 138 (C$_8$H$_{10}$O$_2^+$), 66.

Preparation of Benzyl triethylammonium borohydride[42]

Sodium borohydride (1.135 g, 30 mmol) and benzyltriethyl ammonium chloride (4.54 g, 20 mmol) were separately dissolved in minimum amount of 5M sodium hydroxide solution. This solution of sodium borohydride was mixed with a solution of benzyltriethyl ammonium chloride and stirred for 10 minutes. Dichloromethane and water (2 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous potassium carbonate and filtered over a fluted filter paper. The solvent was evaporated to afford solid quarternary ammonium borohydride. The crude solid was washed with ether and decanted. Pure colorless solid obtained (3.977 g, 96.5%) was dried under vacuum. This solid being slightly hygroscopic has to be stored in a tightly stoppered bottle.

m.p.   : 145-147°C.

Reaction of spirolactone 33 with benzyltriethylammonium borohydride and chlorotrimethylsilane

Benzyltriethylammonium borohydride (2.095 g, 10.17 mmol) in dichloromethane (10 mL) was added dropwise at 0°C to spirolactone 33 (2.075 g, 10.17 mmol) in dichloromethane (10 mL). To this stirred solution, chlorotrimethylsilane (1.105 g, 10.17 mmol, 1.29 mL) in dichloromethane (5 mL) was added dropwise. After allowing the reaction to come to room temperature 1-2 h, dichloromethane was evaporated under vacuum, aqueous potassium carbonate solution was added and extracted with chloroform (2x50 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated to afford the crude compound which was further purified by flash chromatography over silica gel (ethyl acetate : petroleum ether, 6:4) to yield the spirolacto alcohol 34 and 34a (1.524 g, 67.5%), as a mixture of regioisomers. 34 and 34a were not separated but used in the next step as a mixture.

IR (neat)   : 3400, 3050, 2960, 2880, 1750 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.0-2.28 (m, 12H), 2.28-2.81 (m, 3H), 2.81-3.41
                       (m, 2H), 3.81-4.26 (m, 1H).

Oxidation of 34 with pyridinium chlorochromate

To a stirred solution of 34 (0.809 g, 3.644 mmol) and Celite (3.2 g) in dichloromethane (30 mL) was added pyridinium chlorochromate (1.571 g, 7.288 mmol). After 1 h, dichloromethane was evaporated under vacuum, ether (75 mL) was added and filtered

over a pad of Celite.   This was washed with ether (25 mL), sol-
vent evaporated and the crude product was purified by flash
chromatography over silica gel (40% ethyl acetate in petroleum
ether) to afford 35 (0.305 g) and 35a (0.208 g).

The physical data for 35 are as follows :

m.p.   : 154-156^{0}C.

IR (KBr)   : 2955, 2875, 1750, 1735 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.45-2.06 (m, 10H), 2.17 (s, 2H), 2.86 (d, 1H),

                      2.89-3.25 (m, 2H), 3.34-3.63 (m, 1H).

Ms (m/e)   : 221(M+1), 220(M$^+$), 192, 134, 133, 108, 91,

                      80, 66.

Anal. for

C$_{13}$H$_{16}$O$_3$: Calcd. C, 70.91; H, 7.27.

                      Found C, 70.85; H, 7.18.

The physical data for 35a are as follows :

m.p.   : 144-145°C.

IR (KBr)   : 2970, 1755, 1740 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.41-2.11 (m, 10H), 2.20 (brs, 2H), 2.64-2.95

                      (m, 2H), 3.03 (br d, 1H), 3.35-3.63 (m, 1H).

Ms (m/e)   : 221(M+1), 220(M$^+$), 192, 135, 108, 66.

Anal. for

C$_{13}$H$_{16}$O$_3$: Calcd. C, 70.91; H, 7.27.

                      Found C, 70.76; H, 7.09.

Rearrangement of 35 with methane sulfonic acid and phosphorus pentoxide

To a stirred solution of 35 (0.409 g, 1.859 mmol) in methanesulfonic acid (13.33 g, 136.7 mmol, 9 mL) was added phorphorus pentoxide (1.97 g, 13.87 mmol) and the stirring was continued at room temperature for 2 h. Water (10 mL) was carefully added and the reaction mixture was extracted with chloroform. The organic layers were successively washed with water, sodium bicarbonate solution and brine and dried over anhydrous sodium sulfate. The crude product obtained on evaporating the solvent was purified by flash chromatography over silica gel to afford 36 (0.203 g, 54%) as an oil.

The physical data for 36 are as follows :

IR (neat)   : 3060, 1740, 1685, 1620 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.58-1.91 (m, 2H), 1.98 (br s, 2H), 2.25 (m, 7H), 2.77 (brs, 1H), 3.0 (m, 1H), 3.31 (m, 1H).

Ms (m/e)   : 203(M+1), 202(M^{+}), 135, 134, 133, 120, 117, 91.

Anal. for

$C_{13}H_{14}O_2$: Calcd. C, 77.23; H, 6.93.

                         Found C, 77.18; H, 6.84.

Rearrangement of 35a with methane sulfonic acid and phosphorus pentoxide

Compound 35a (0.15g, 0.682 mmol) in methanesulfonic acid (5.18 g, 53.94 mmol, 3.4 mL) phorphorus pentoxide (0.776 g, 5.39 mmol) under similar reaction conditions, as mentioned above afforded 36a (0.072 g, 52%) as an oil.

The physical data for <u>36a</u> are as follows :

IR (neat)   : 2980, 1745, 1690, 1625 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 1.5-1.91 (m, 2H), 1.98 (br s, 2H), 2.30 (m, 7H),

                        2.68-2.97 (m, 1H), 3.0 (s, 1H), 3.31 (m, 1H).

<u>Anal</u>. <u>for</u>

C$_{13}$H$_{14}$O$_2$: Calcd. C, 77.23; H, 6.93.

                        Found C, 77.14; H, 6.76.

Reaction of <u>36</u> with m-chloroperbenzoic acid

    To a stirred solution of <u>36</u> (0.06 g, 0.297 mmol) in dichloromethane (5 mL) was added m-chloroperbenzoic acid (0,061 g, 0.356 mmol) and p-toluenesulfonic acid (0.045 g, 0.238 mmol). After 48 h, dichloromethane was evaporated and the crude compound was taken in chloroform and washed with sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. The crude compound obtained after evaporation of the solvent was purified by flash chromatography over silica gel (60% ethyl acetate in petroleum ether) to afford the unreacted starting material <u>36</u> (0.04 g). Further elution with (80% ethyl acetate in petroleum ether) afforded the lactoenone <u>37</u> (0.017 g, 78%).

IR (neat)   : 2960, 1735, 1685, 1625 cm^{-1}.

^{1}H NMR (CDCl$_3$)   : 1.67-1.89 (m, 2H), 2.06 (br s, 2H), 2.36

                        (br s, 4H), 2.60 (d, 1H), 2.75-3.06 (m, 1H),

                        3.43 (bd, 3H), 4.31 (d, 1H, J=7.5 Hz).

II.4.c INTERMOLECULAR CYCLOADDITION APPROACH
(ENDO-DICYCLOPENTADIENE ROUTE)

Endo-dicyclopentadiene (2.045 g, 15.47 mmol) and triethyl-amine (1.821 g, 18 mmol, 2.5 mL) were taken in petroleum ether (40-60°C, 40 mL) and gently refluxed. To this dichloroacetyl chloride (2.137 g, 14.5 mmol, 1.4 mL) in petroleum ether (40-60°C, 20 mL) was added dropwise over a period of 0.5 h. After the addition was over, it was refluxed for an additional two hours. Water (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with ether (2x20 mL). The organic layers were combined and washed with brine, water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product obtained was purified by flash chromatography over silica gel (ether:petroleum ether, 2:98) to recover unreacted starting material (0.673 g). Further elution (ether : petroleum ether, 5:95) afforded the adduct **39** (1.262 g, 50%) as a colorless solid.

m.p.	: 54-55°C (lit.[34] m.p. 54-55°C).
IR (CHCl$_3$)	: 3070, 2990, 2960, 2890, 1805 cm^{-1}.
^{1}H NMR (CDCl$_3$)	: 1.42 (dd, 2H), 1.78 (dd, 2H), 2.86 (d, 2H), 3.04 (m, 2H), 3.20 (m, 1H), 3.54 (m, 1H), 6.20 (t, 2H).
Ms (m/e)	: 245, 243, 148, 141, 113, 66.
Anal. for	
C$_{12}$H$_{12}$OCl$_2$	: Calcd. C, 59.26; H, 4.94.
	Found C, 59.18; H, 4.86.

Ring expansion of 39 with diazomethane

Diazomethane generated from `Diazald' (3.8 g), was added in portions to a stirred solution of 39 (1.262 g, 5.193 mmol) in ether (5 mL) at 0°C. Progress of the reaction was monitored periodically by TLC for 1-2 h. Excess diazomethane in the reaction was destroyed by the addition of a few drops of acetic acid. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with (2X25 mL) portions of ether. The combined ethereal extracts were successively washed with saturated sodium bicarbonate solution, water, brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product 40 thus obtained was used in the next step without further purification.

Dehalogenation of 40 using zinc/acetic acid

Compound 40 in acetic acid (7.6 mL) was treated with zinc powder (2.17 g) and heated at 70°C for 1 h. After cooling, ether (35 mL) and water (20 mL) were added and the organic layer was separated. The aqueous layer was further extracted with ether (2X30 mL) and the combined organic layers were successively washed with sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. The crude product thus obtained on evaporation of the solvent was purified by flash chromatography (ether : petroleum ether, 1:9) over silica gel to afford 41 (0.657 g, 67%) as a pale yellow solid.

m.p.   : 71-72°C,

IR (KBr)   : 3050, 2960, 1735 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.29-1.59 (m, 4H), 1.87-2.07 (m, 4H), 2.07-2.56 (m, 2H), 2.56-3.0 (m, 4H), 6.20 (s, 2H).

Ms (m/e) : 189(M+1), 188(M$^+$), 123, 122, 66.

<u>Anal. for</u>

C$_{13}$H$_{16}$O : Calcd. C, 82.98; H, 8.51.

Found C, 82.74; H, 8.38.

Oxidative cleavage of 41 with KMnO$_4$/CuSO$_4$

To a stirred solution of <u>41</u> (0.098 g, 0.52 mmol) in dichloromethane (3 mL) was added a well pulverized mixture of potassium permanganate : copper sulfate : t-Butanol : water in the ratio (1 g : 0.5 g : 0.25 mL : 0.1 mL). After 1.5 h the reaction mixture was filtered over a pad of Celite and washed with ether (30 mL). The solvent was evaporated and the crude product thus obtained was purified by flash chromatography over silica gel (ethyl acetate : petroleum ether 1:1) to afford the pure dialdehyde <u>42</u> (0.06 g, 52%).

IR (neat) : 2940, 2720, 1720, 1400 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.69-1.91 (m, 6H), 1.91-2.51 (m, 6H), 2.51-2.79 (m, 2H), 9.88 (6, 2H, J=3.75 Hz).

II.4.d Intramolecular vinylketene-olefin cycloaddition approch

Preparation of (carbethoxymethyl)triphenylphosphonium bromide 62

Bromoethyl acetate (16.7 g, 0.1 mol) in benzene (20 mL) was added dropwise to a stirred solution of triphenylphosphine (25 g, 0.095 mole) in benzene (40 mL) at room temperature. A white precipitate formed immediately and stirring was continued

for a further 2 h. The solid obtained, was filtered over a Buchner funnel, washed with benzene and dried to afford the phosphonium salt 62 (37.2 g).

m.p.   : 156-158°C (lit.[40] m.p. 158°C)

Preparation of (carbethoxymethylene)triphenylphosphorane 63

To a stirred solution of the phosphonium salt 62 (37 g) in water (70 mL) and a drop of phenophthalein was added dropwise 10% sodium hydroxide solution until the pink colour just disappeared. The resulting ylid precipitates out as a colorless solid. It was filtered over a Buchner funnel and was washed well with water. The crude product thus obtained, was recrystallized from ethyl acetate-petroleum ether to obtain a colorless solid in (28 g) 85% yield.

m.p.   : 125-126°C (lit.[40] m.p. 129-130°C).

Preparation of 5-hexen-2-one 53[35]

A mixture of acetylacetone (11 g, 0.11 mol), freshly distilled allyl bromide (12.1 g, 0.1 mol) and anhydrous potassium carbonate (16 g, 0.115 mol) in absolute ethanol (60 mL) was refluxed for 18 h. Ethanol (~ 50 mL) was distilled off, the residue was cooled and ice-cold water (120 mL) was added to dissolve all the salt. It was then extracted with ether and the ether extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was distilled to yield 5-hexen-2-one 53 (5.5-5.6 g, 52%).

b.p. : 126-127°C/atm. (lit.[35] b.p. 129°C/atm).

IR (thin film) : 3080, 1715, 1640 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 2.14 (s, 3H), 2.24 - 2.64 (m, 4H), 4.9 - 5.14 (m, 2H), 5.6 - 6.04 (m, 1H).

Preparation of ethyl-3-methyl-2,6-heptadienoate 54

A mixture of 5-hexen-2-one 53 (2 g, 20.4 mmol), Wittig reagent 63 (7.656 g, 22 mmol) and benzoic acid (0.61 g, 5 mmol) in dry benzene (100 mL) was refluxed under nitrogen for 16 h. Benzene (85 mL) was distilled off and the precipitated triphenyl-phosphine oxide was filtered over a pad of Celite. The crude ester 54 thus obtained, was directly used in the next step without purification.

IR (thin film) : 3060, 2960, 2940, 1720, 1650 cm^{-1}.

Hydrolysis of ethyl-3-methyl-2,6-heptadienoate 54

A solution of the crude ester 54 (2.2 g) in methanol (5 mL) was added 10% methanolic sodium hydroxide solution (20 mL) and stirred at room temperature for 20 h. The reaction was monitored by TLC. The reaction mixture was diluted with water (50 mL) and extracted with ether to recover any unhydrolyzed ester. The aqueous layer was neutralised with 10% hydrochloric acid solution and extracted with chloroform (3x50 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate and the solvent was evaporated to afford 55 (1.2 g, 42%) as a mixture of E and Z isomers.

IR (thin film) : 3080, 2980, 2930, 1690, 1640 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.92 (d, 3H), 2.17 (d, 3H), 2.26 (m, 4H),

2.75 (t, 2H), 4.95-5.05 (m, 2H), 5.08 (t, 2H),

5.70 (s, 1H), 5.8 (m, 1H).

Preparation of 4-methylbicyclo[3.2.0]hept-3-en-6-one 57
Method A

To a stirred solution of the α,β-unsaturated acid 55 (0.15 g, 1.07 mmol) in dry benzene (5 mL) was added dry acetic anhydride (0.218 g, 2.14 mmol, 0.2mL) and 4-N,N-dimethylaminopyridine (0.261 g, 2.14 mmol) and refluxed for 16 h. The reaction mixture was cooled, ether (20 mL) and water (5 mL) were added and the organic layer was separated. It was washed with saturated sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product thus obtained was purified by flash chromatography over silica gel (ethyl acetate : petroleum ether, 5:95) to afford 57 (0.35 g, 27%).

IR (neat)   : 3080, 2980, 2940, 1780, 1640, 1450 cm^{-1}.
^{1}H NMR (CDCl$_3$) : 1.68 (s, 3H), 2.36 (br, 1H), 2.5-2.84 (m, 3H),

3.0-3.4 (m, 1H), 4.0 (br, 1H), 5.56 (br, 1H).

Ms (m/e)   : 122(M$^+$).

Preparation of 4-methylbicyclo[3.2.0]hept-3-en-6-one 57
Method B

The α,β-unsaturated carboxylic acid 55 (0.27 g, 1.92 mmol) on treatment with acetic anhydride (1.56 g, 15.36 mmol, 1.45 mL) and 4-N,N-dimethylaminopyridine (0.351 g, 2.88 mmol) in dry

benzene (5 mL) under similar reaction conditions (16 h) gave <u>57</u> (0.12 g, 51%).

IR (neat)   : 3080, 2980, 2940, 1780, 1640, 1450 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 1.68 (s, 3H), 2.36 (br, 1H), 2.5-2.84 (m, 3H), 3.0-3.4 (m, 1H), 4.0 (br, 1H), 5.56 (br, 1H).

Ms (m/e)   : 122(M$^+$).

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